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Apr. 11, 1978

Method and apparatus for pulmonary function analysis

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"The Beckman Bulletin", vol. II, No. 2, 1967, pp. 1 & 7.

PRIM-EXMR: Michell, Robert W.

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LEGAL-REP: Fitch, Even, Tabin & Luedeka

ABST:
A method and apparatus for analyzing pulmonary function including diffusing capacity and cardiac output or local pulmonary blood flow while necessarily determining alveolar volume in order to complete the above-noted analysis. In order to provide a rapid response in each of the abovenoted analyses or determinations, appropriate gases are caused to be inhaled and exhaled through a sample cell wherein a percentage of each gas may be constantly monitored during inhalation and exhalation by means of non-dispersive infrared absorption techniques, the sample cell and associated components of the pulmonary function analyzing device including additional features to facilitate the abovenoted analyses and determinations, the combination of gases employed for monitoring the pulmonary functions being selected to permit accurate detection by infrared absorption techniques.

NO-OF-CLAIMS: 20

EXMPL-CLAIM: <=15> 1

NO-OF-FIGURES: 6

NO-DRWNG-PP: 3

SUM:

BACKGROUND OF THE INVENTION

The present invention relates to a method and apparatus for analyzing pulmonary functions and more particularly to such a method and apparatus wherein the functions are analyzed through simultaneous infrared radiation monitoring of a plurality of gases, each selected in accordance with its ability to indicate a separate one of the pulmonary functions.

The analysis of gases being inhaled or exhaled from the lungs has long been employed in the assessment of various pulmonary functions. Possibly the most important or basic of these functions includes the determination of alveolar volume or capacity. This function in itself provides an indication as to the condition of the lungs and in addition is essential for the proper measurement or analysis of additional functions such as pulmonary diffusing capacity and cardiac output as manifested in pulmonary blood flow. However, the techniques employed for monitoring these functions have been time consuming while requiring substantial and generally immobile equipment tending to prevent or impair the ability to fully assess various pulmonary functions. In order to provide a more accurate background for the present invention, the general techniques for assessing each of these functions are described briefly below followed by a discussion of problems presently existing in the prior art which prevent the maximum utilization of pulmonary function analysis.

As indicated above, the measurement of alveolar volume may be employed to assess pulmonary function and in itself provides an index of the severity, or at least changes in severity, of certain patterns of pulmonary function. In addition, an accurate determination of lung volume is essential for the proper understanding of newly recognized patterns of dysfunction which in turn are

becoming essential for a number of dynamic (and more substantive) studies of pulmonary function in establishing conditions of health and disease. For example, the measurement of pulmonary diffusing capacity by the single breath method can be no more reliable than the underlying measurement of lung volume. Similarly, the single breath method of assessing pulmonary blood flow is dependent upon the underlying measurement of lung volume.

A simple and commonly known method for measuring alveolar volume consists in causing a patient to inhale a known concentration of an inert and insoluble gas such as helium or neon. After a short selected period of breath-holding to allow uniform distribution of the inhaled gas throughout the lungs, the breath is exhaled and a sample of the exhaled gas is collected and analyzed to determine the concentration of the inert gas, for example by means of a gas chromatograph or mass spectrometer. The resultant determination of the gas dilution ratio between the inhaled and exhaled gases may be employed along with volume determinations of the inhaled and exhaled gases in order to assess the alveolar volume. However, these techniques for measuring alveolar volume have serious disadvantages.

Initially, gas chromatography techniques may take as much as ten minutes to perform under usual pulmonary function laboratory conditions with the analysis being limited to a selected point in time during exhalation. In addition, the need for a gas collection system and chromatograph tends to preclude mobile mass screening programs.

A mass spectrometer provides an effective and portable system. However, as is discussed in greater detail below, the mass spectrometer is itself expensive and commonly requires the use of expensive, rare isotope gases.

The measurement of the diffusing capacity of the lungs has similarly become a useful technique in the diagnosis of pulmonary vascular obstruction, pulmonary fibrosis and subclinical emphysema and accordingly may be used as a screening test for determining general pulmonary condition. In a single breath method for determining diffusing capacity, the subject or patient inhales to vital capacity a low, non-toxic concentration in air of a suitable gas such as low concentration carbon monoxide along with an insoluble and inert tracer gas as described above in connection with the measurement of lung volume.

After the breath is held for a short selected period of for example ten seconds, the subject exhales into a collection means such as a spirometer. The exhaled gas is sampled after a prescribed volume of exhalation with the concentrations of the two test gases in the expirate being determined, for example, by means of gas chromatography.

In this manner, it is possible to calculate alveolar volume as described above by means of the dilution ratio for the inert gas. At the same time, pulmonary diffusing capacity may be determined from the initial concentration of carbon monoxide inhaled into the lungs and the calculated diffusion of carbon monoxide from the lungs between inhalation and exhalation.

In the abovenoted tests for diffusing capacity, helium and neon have been most frequently employed as the insoluble inert tracer gas. Carbon monoxide is particularly effective in determining the diffusing capacity of the lungs because of its ability to combine with hemoglobin much more effectively than

oxygen; hence, the rate of diffusion of carbon monoxide from the lungs is limited only by its ability to pass through the alveolar capillary walls. Because of its high affinity for hemoglobin, carbon monoxide is a particularly suitable gas for investigating pulmonary diffusing capacity and diffusion abnormalities. Other gases may possibly be employed in place of carbon monoxide for this function. For example, cyanide compounds tend to exhibit the same tendencies of absorption in hemoglobin while being limited in their ability to pass through the alveolar capillary walls. However, such cyanide compounds tend to be unstable as to instant form. In particular such cyanide compounds tend to be present with equilibrium amounts of the monomer (CN) and the dimer (C2N2) as well as its acid form (HCN). Accordingly, such cyanide compounds are difficult to employ within the abovenoted technique which is normally carried out using carbon monoxide.

In connection with the measurement of diffusing capacity, it is noted that the test is relatively simple, noninvasive and painless but does require a skilled operator and expensive equipment to provide reliable data. Since the method also requires collection of an expired alveolar gas sample for subsequent analysis, the diffusing capacity may be determined only for a single point in the expiration profile. Multiple points during a single breath may be analyzed for example with increased complexity by taking multiple samples. However, reproducibility with such a technique is relatively poor. Accordingly, the sampling requirement within this technique as well as the slow response time of the standard instruments used in the measurements of expired gas concentrations tend to detract from its value as a diagnostic tool in mass screening.

A different but related method for measuring pulmonary diffusing capacity employs a respiratory mass spectrometer with the carbon monoxide being selected as the isotopic form (<13> C<16> O or <12> C<18> O) having the mass numbers of 29 or 30 respectively, to enable ts separation from molecular nitrogen with a mass number of 28, which is identical to that of the common isotope (<12> C<16> O). This method, which permits continuous measurement of the expired gases, enables a determination of the distribution of the diffusing capacity during a single breath and may thus be employed for obtaining more complex diagnostic information. However, it does require expensive equipment and the use of a rare isotopic form gas of limited availability. These factors tend to make the technique prohibitively expensive for routine clinical use.

The abovenoted methods of assessing diffusing capacity also fail to provide a rapid response for the assessment of the amount of carbon monoxide in the exhaled gas at any instant. Accordingly, these methods of measuring diffusing capacity are inadequate for certain diagnostic purposes, in particular, the determination of diffusing capacity during exercise where the rate of diffusion must be instantly monitored across a substantial profile portion of exhalation.

It has also been known that the analysis of respired gases may be employed to measure cardiac output or local pulmonary blood flow. In particular, it has been known for some time that gaseous acetylene in small concentrations may be measured during inhalation and exhalation, also in a single breath method, to determine the rate of blood flow in the capillary walls of the lungs. This test depends upon the ability of the acetylene gas to readily pass through the alveolar capillary walls while having only limited solubility in blood. Accordingly, the rate at which acetylene is internally absorbed by the body from the lungs depends upon the rate at which blood is made available for its

absorption. Here again, acetylene is used in combination with an inert gas of the type discussed above to permit a simultaneous assessment of alveolar volume in order to calculate the actual rate of loss of acetylene from the lungs as determined by pulmonary blood flow.

The abovenoted technique of pulmonary analysis for assessing blood flow has been used only to a limited extent because of the more developed and thus more commonly employed technique, at least to date, of cardiac catheterization based upon oxygen absorption. However, pulmonary testing with acetylene is of particular advantage in that it is noninvasive and may be adapted to provide an instantaneous measurement of blood flow through the gas exchanging surfaces of walls in the lungs.

It may be seen that various techniques are presently known for accomplishing the determination of alveolar volume as well as the determination of pulmonary diffusing capacity and pulmonary blood flow, for example. However, it has not heretofore been possible to rapidly accomplish various combinations of these determinations with simple portable equipment having a rapid response for assessing the particular pulmonary functions across the entire expiration profile.

There has thus been found to remain a need for a method and apparatus for more rapidly and conveniently assessing pulmonary functions such as those noted above in order to permit the use of such tests in routine clinical use for example as a screening tool.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the invention to provide a method and apparatus for accomplishing pulmonary function analysis in a noninvasive manner and with rapid response to facilitate use of the method and apparatus for assessing instantaneous pulmonary functions.

It is a more particular object of the invention to provide such a method and apparatus wherein analysis of the pulmonary functions is accomplished through the monitoring of selected gases during inhalation and exhalation by means of non-dispersive infrared absorption techniques.

It is a more specific object of the invention to provide such a method and apparatus for simultaneously monitoring alveolar volume and pulmonary diffusing capacity, for simultaneously monitoring alveolar volume and pulmonary blood flow, or for simultaneously monitoring the three functions of alveolar volume, plumonary diffusing capacity and pulmonary blood flow.

It is an even more specific object of the invention to provide such a method and apparatus of pulmonary function analysis wherein two or more selected gas components may be monitored by inhalation and exhalation through an infrared analyzer sample cell including means for simultaneously and continuously monitoring the percentages of the selected gases during inhalation and exhalation.

It is a further related object of the invention to provide such a method and apparatus wherein the abovenoted sample cell includes means for assessing volume flow during inhalation and exhalation as well as means for assisting in the determination of alveolar volume.

Yet another further related object of the invention is to provide such a method and apparatus wherein the two or more selected gases for monitoring the various pulmonary functions are selected with closely related but distinct bands
of infrared absorption to permit their simultaneous monitoring within the sample cell.

Still another object of the invention is to provide such a method and apparatus wherein the sample cell also includes means to adjust for the effective temperature upon the determination of the gas concentrations.

Still another object of the invention is to provide such a method and apparatus including additional means for monitoring the concentration of interferent gases such as water vapor during inhalation and exhalation in order to properly adjust the determinations for the abovenoted pulmonary functions.

In summary, the present invention involves the monitoring through infrared radiation techniques of a first inert gas which permits the determination of alveolar volume by detecting the dilution effect of the inert gas being inhaled into the lungs and then exhaled. A second gas, providing a means for monitoring an additional pulmonary function, is inhaled along with the inert gas and simultaneously monitored by the same infrared radiation techniques to provide an assessment of the additional function, for example pulmonary diffusing capacity or pulmonary blood flow.

In order to facilitate simultaneous monitoring of two or three selected gases, a sample cell is contemplated through which the gases are commonly inhaled and exhaled with continuous monitoring by means of infrared radiation. The sample cell is designed with limited volume for more rapid response and preferably includes pressure drop means for simultaneously determining the rate and volume of gas flow during inhaltion and exhalation. Finally, the gases employed for the various pulmonary functions being analyzed are carefully selected to have closely related but distinct infrared absorption bands to faclitate their simultaneous monitoring within the sample cell. Through the use of such a sample cell, a plurality of electronic channels may be employed to receive data for each of the gases in order to provide a signal output indicative of the respective pulmonary functions.

Additional objects and advantages of the invention will be made apparent in the following description having reference to the accompanying drawings.

DRWDESC:
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a partially sectioned, partially schematic representation of a pulmonary function analyzer device according to the present invention.

FIG. 2 is a fragmentary view of a filter wheel employed within the pulmonary function analyzer device of FIG. 1.

FIG. 2a is a table identifying the various filter elements in the filter wheel of FIG. 2.

FIG. 3 is a schematic representation of an electronic processing unit associated with the pulmonary function analyzer device of FIG. 1.

FIG. 3a is a table identifying various signals labeled by capital letters A through F in FIG. 3.

FIG. 4 is a graphical representation of the infrared spectrum for selected gases employed in the pulmonary function analyzer device of FIG. 1 along with selected interference gases.

DETDESC:

DESCRIPTION OF THE PREFERRED EMBODIMENTS

As indicated above, the present invention provides a method and apparatus for analyzing selected pulmonary functions by means of infrared radiation monitoring of a plurality of gases which are passed through the pulmonary function analyzer device of FIG. 1 during both inhalation and expiration from the lungs. As was also indicated above, the pulmonary function analyzer device of FIG. 1 may be employed to simultaneously and continuously monitor the concentrations of three different gases relating to three different pulmonary functions, preferably alveolar volume, pulmonary diffusing capacity and pulmonary blood flow. However, the pulmonary function analyzer device of FIG. 1 may also be employed to simultaneously perform two different pulmonary functions, preferably the function of determining alveolar volume and either pulmonary diffusing capacity or pulmonary blood flow.

The pulmonary function analyzer of the present invention preferably includes a separate optics unit indicated at 12 in FIG. 1 and an electronic processing unit indicated at 14 in FIG. 3. The electronic processing unit 14 includes generally conventional electronics components and circuits for receiving various signals porvided by the optics unit 12 of FIG. 1, processing those signals and providing an output or display effective to indicate the concentrations of the selected gases. The electronic processing unit 14 of FIG. 3 is described in greater detail below. However, the present summary of the invention is particularly concerned with the optics unit 12 of FIG. 1 and included components such as a filter wheel assembly 16 (see FIGS. 1 and 2) as well as the particular gases employed in combination within the present pulmonary function analyzer.

Generally, the optics unit 12 includes a shaped sample cell 18 which is interconnected with two separate conduits 20 and 22. The conduit 20 is adapted as a mouthpiece for the subject or patient to be tested by the pulmonary function analyzer. The other conduit 22 is of a branched configuration for alternately connecting the sample cell either with a gas supply 24 or a gas exhaust 25.

The optics unit 12 also includes a source of infrared radiation, indicated at 26, at one end of the sample cell 18. A detector assembly 28 is arranged at the other end of the sample cell in order to provide an instant and continuous analysis of gases within the sample cell 18. The filter wheel assembly 16 is mounted to selectively intercept the infrared radiation signal generated by the source 26.

In further summary as to operation of the pulmonary function analyzer device,

the subject inhales through the mouthpiece 20 and draws a gas of selected composition from the supply 24 through the sample cell 18. The inhaled gas may be retained in the lungs of the subject for a selected period of time to permit uniform dilution of the inhaled gas throughout the lungs. Thereafter, the subject exhales again through the sample cell 18 with the exhaled gases either being exhausted through the outlet 25 or collected by suitable means (not shown) if it is desired to further analyze the exhaled gases.

In any event, the source 26 generates infrared radiation through the sample cell which is attenuated by the infrared absorption bands of gases in the sample cell 18 and thereafter received by the detector assembly 28. Thus, the detector assembly 28 generates an electrical signal providing a means of clearly and instantly identifying the concentration of the selected gases within the sample cell at all times during both inhalation and exhalation.

As noted above, the simultaneous analysis of gases in the sample cell 18 by the detector assembly 28 may be based upon three different gases relating to three different pulmonary functions such as alveolar volume, pulmonary diffusing capacity and pulmonary blood flow. However, the device may also be employed to simultaneously monitor any two of the gases, for example, those associated with alveolar volume and either pulmonary diffusing capacity or pulmonary blood flow.

As will be described in greater detail below, the detector assembly 28 may also be employed to additionally analyze the concentration of water vapor within the sample cell 18 in order to more accurately calibrate the output of the pulmonary function analyzer through the electronic processing unit 14 of FIG. 3.

Selection of Gases

The selection of the various gases employed within the pulmonary function analyzer of the present invention is of particular importance within the present invention. All of the gases relating to the various pulmonary functions must each exhibit an effective infrared radiation absorption band of usable strength in order to develop a response by the present pulmonary function analyzer. For example, the standard gases employed in the prior art for the measurement of the lung volume, such as helium, neon, and argon, do not absorb infrared radiation and accordingly may not be employed in the present pulmonary function analyzer.

In addition, each of the gases must exhibit the necessary reaction within the lungs for providing an indication of the particular pulmonary function to be monitored. An analysis of the particular gases employed in the pulmonary function analyzer is set forth immediately below. However, it is first generally noted that the composite gas being exhaled by a patient or subject may include other gases from the lungs which must also be considered in the design of the pulmonary function analyzer. For example, certain gases which are commonly present in the lungs tend to interfere with infrared detection of the selected gases. Accordingly, the selected gases identified with the various pulmonary functions are also selected to permit monitoring of varying concentrations thereof even in the presence of such interferent gases.

At the same time, the gases associated with the various pulmonary functions must also be considered as interferent gases relative to each other. Accordingly, the selected gases must generally have distinct absorption bands or

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wave lengths so that they will not interfere with each other.

Finally, it is also important to ascertain the combined wave length or absorption band for all of the gases associated with the various pulmonary functions. If the combined absorption band of the gases is overly broad, the design of the optics unit 12 may tend to be complex. For example, the use of selected gases with a very broad band of wave lengths might require the inclusion of beam splitter means in the optics unit for separating different ranges of wave lengths which would then be analyzed by separate detector assemblies.

Returning again to the selection of the gases associated with the varous pulmonary functions, a gas for determining alveolar volume must be inert while exhibiting a useful absorption band for infrared radiation in accordance with the preceding comments. As noted above, the usual inert gases such as helium, neon and argon may not be employed since they do not absorb infrared radiation. However, two exemplary inert gases exhibiting infrared absorption bands are sulfur hexafluoride (SF6) and methane (CH4).

Sulfur hexafluoride exhibits a detectable absorption band for infrared radiation. Tests with a pulmonary function analyzer device have indicated the feasability of employing sulfur hexafluoride for determining alveolar volume. However, it has also been found that the absorption band of sulfur hexafluoride is not at a wavelength which can be detected by the same detector used for carbon monoxide. A separate special detector could be and has been used to detect sulfur hexafluoride. However, it has been found more expedient to employ methane for monitoring this pulmonary function.

A careful study has indicated that methane satisfies both the physiological and detection criteria for use in the present invention. Methane exhibits a strong infrared radiation absorption band centered at 3.2 mu m (millimicrons) which absorption band is substantially free from interference caused by water vapor and carbon dioxide, two of the interferent gases present in the lungs.

Some overlap exists between the absorption band for methane and the absorption band typical of longer chain hydrocarbons which lie in the general absorption band of 3.3 to 3.7 mu m. Of such hydrocarbon compounds, only ethanol (C2H5OH) appears to provide any potentially significant interference. However, a more detailed investigation of the interaction between the spectra for ethanol and methane indicates that any such interference is relatively insignificant in the results provided by the present pulmonary function analyzer. Also, the problem of interference with ethanol may be controlled to some degree by limiting the consumption of alcohol prior to conducting tests with the present pulmonary function analyzer.

As for the physiological effect of methane, it is relatively insoluble either in water or hemoglobin and is therefore not substantially diffused through the alveolar capillary walls.

For the monitoring of pulmonary diffusing capacity, it is initially noted that a completely different physiological effect is required of a gas employed for this purpose. Initially, the gas must tend to be readily absorbed by hemoglobin so that its absorption in the blood will not be a relatively limiting factor determining its diffusion from the lungs. Rather, the gas should also

exhibit a relatively controlled but well characterized rate of absorption or diffusion through the alveolar capillary walls. In this manner, the rate of flow for the gas from the lungs tends to be directly proportional with the function of pulmonary diffusing capacity and thus an effective means for monitoring that function.

As discussed in some detail above, cyanide compounds may also be employed for monitoring this partiuclar pulmonary function. However, because of certain problems associated with the monitoring of cyanides, carbon monoxide is preferred for use within the pulmonary function analyzer of the present invention.

As may be seen by reference to FIG. 4, the infrared radiation absorption band for carbon monoxide is approximately 4.5 to 4.75 mu m. Accordingly, carbon monoxide in a preferred maximum concentration of about 0.3% is employed within the gas supply indicated at 24 in FIG. 1. Such a concentration has been found to exhibit acceptably low toxicity for use in the manner of the present invention.

Finally, in assessing or monitoring the function of cardiac output or pulmonary bloodflow, acetylene (C_2H_2) is particularly contemplated for use within the present invention. Acetylene has been found to ideally exhibit the desired physiological effects for monitoring this function. In particular, acetylene has well characterized solubility in blood. In addition, acetylene is readily diffused through the alveolar capillary walls or surfaces of the lungs so that dissipation of acetylene from the lungs may be directly correlated with capillary blood flow in the lungs. In addition, acetylene is otherwise effectively inert, so that its solubility would not be influenced by hematocrit. At the same time, acetylene is effectively incapable by itself of influencing pulmonary blood.

Other gases such as nitrous oxide and ethylene have been considered for monitoring this function because of their intermediate solubility in blood and lung tissue. However, certain problems have been found in connection with each of these gases so that acetylene is preferred. For example, nitrous oxide is one of the few gases which strongly interferes with carbon monoxide detection by means of infrared radiation.

Some minor problems have been found, for example, in connection with acetylene storage since the gas tends to leak through rubber which is commonly employed within such devices. However, this problem may be readily controlled through the use of suitable linings within the pulmonary function analyzer device of the present invention and associated components.

Acetylene also satisfies the spectral criteria of the present invention since the primary infrared radiation absorption band centered at approximately 3.5 mu m lies well within an "interference-free" window as illustrated in FIG. 4. In particular, the spectrum of acetylene does not significantly overlap that of methane and with a judicious choice of filter specifications and electronics compensation in the circuitry described below, total separation of the signals for these two gases may be effectively achieved.

The preceding description is intended to establish the preferred selection of methane, carbon monoxide and acetylene for measuring the respective pulmonary functions of alveolar or lung volume, pulmonary diffusing capacity and pulmonary

blood flow. In order to more clearly illustrate the associated absorption bands for these three gases, reference is again made to FIG. 4 wherein the absorption bands for the three gases are illustrated in conjunction with representations of the major absorption regions for the dominant interferent gases, carbon dioxide and water vapor. Also, it may be seen from FIG. 4, that the overall combined band width of approximately 3 to 4.7 mu m which includes all of the above three gases, is of sufficiently limited scope to permit detection of infrared radiation absorption for all three gases by means of a single detector unit as indicated at 28 in FIG. 1.

Description of Optics Unit (FIG. 1)

Referring now to FIG. 1, it was noted above that gas ports or conduits 20 and 22 are provided at opposite ends of the same cell 18. The conduit 20 provides a mouthpiece while the conduit 22 provides alternate communication with either an exhaust or a source of gas supply.

Optical windows 30 and 32 formed for example from calcium fluoride or sapphire are arranged at opposite ends of the sample cell to provide an enclosure therebetween for the passage of inhaled and exhaled gases. The window 30 is arranged adjacent the source 26 and the chopper wheel assembly 16 while the other window 32 is arranged adjacent the detector assembly 28.

The manner of generating and detecting a number of IR band widths is commonly referred to as the "filter wheel" technique. Briefly, the filter wheel assembly 16 includes a chopper wheel 34 which is rotatable by motor means 36. As may be more clearly seen in FIG. 2, the chopper wheel 34 mounts six filter elements respectively identified as A, B, C, D, E and F. The function of these various filters is described below. However, the filters are arranged so that upon rotation of the chopper wheel 34, they intersect or are periodically aligned between the IR source 26 and the sample cell 18.

The filters B, C and F correlate with the absorption bands for the respective gases CH4, C2H2, and CO, the filter pass band for the filters being selected to include a strong absorption band of the associated gas to be detected.

In addition, the filter D provides a span reference at a wave length which is not absorbed by any of the three test gas components. The reference pulse from the filter D is electronically employed to provide an overall transmission amplitude or span reference which renders the instrument insensitive to variations in window transmission, sample cell reflectivity, etc. As will be made apparent in the discussion of the electronic processing unit 14 illustrated in FIG. 3, the span reference pulse is employed as a reference base for correcting or calibrating the signal output for the three filters B, C and F.

An opaque plate at filter position A is employed to provide a zero beam reference for the measurement of the radiation pulse amplitude from the three filters B, C and F. The zero reference pulse provided at the position A is required since the radiation pulses from the other filters tend to follow each other so closely that there may be insufficient spacing between them for the effective establishment of a noise-free zero reference.

The filter E is selected to cover the band width for water vapor. Although the pulmonary function analyzer of the present invention particularly contemplates monitoring of the three gases carbon monoxide, methane and

acetylene, it also preferably monitors water vapor as well in order to provide a corrections factor for those three gases in order to more accurately calibrate the output signals from the pulmonary function analyzer. The filter E permits an interference-free measurement of water concentration at the wave length of 2.6 mu m with a band width of 0.07 mu m in order to avoid parasitic response to the CO2 band at 2.7 mu m (see FIG. 4).

It is incidentally noted that, rather than providing a similar filter for monitoring CO2 concentration, it is possible to substantially reduce instrument response to CO2 by inserting a CO2 absorbing cell (not shown) in the optical path. This could be accomplished, for example, by filling the chamber 35 formed between the window 32 and the detector assembly 28 with carbon dioxide (CO2) or any other selected interferent gas. In this manner, all infrared radiation which would be susceptible to absorption because of the presence of the selected interferent gas in the sample cell is removed in order to permit more accurate detection of gases in the sample cell. Carbon dioxide is of particular concern since it is commonly present in an expired gas mixture.

An optical pick-up unit 38 is also associated with the chopper wheel 34 for synchronizing pulses from each of the filters A-F with the electron processing unit 14. The optical pick-up unit 38 includes a light emitting diode means 40 on one side of the chopper wheel 34 with a photo transistor 42 being arranged upon the side of the chopper wheel 34. Referring momentarily to FIG. 2, it may be seen that a pair of pick-up holes 44 is associated with each of the filters. As each of the pick-up holes passes the optical unit 38, the photo transistor 42 is actuated by the light emitting diode 40 to produce a synchronizing signal for the electronic processing unit 14.

In order to assure that counter means (not otherwise shown) within the electronic processing unit 14 remain in synchronization with the chopper wheel 34, a reset pulse is generated by a single reset hole 46 provided adjacent the center of the filter position A. Thus, a reset pulse succeeds the start pulse for the filter position A more rapidly than any other pulse in the entire cycle. This reset pulse may be distinguished for example by means of a timer and coincident circuit (not shown) to generate the counter reset pulse.

The reset unit also serves a safety function of protecting the filter wheel from steady infrared radiation which would become destructively intense for any of the filters A-F if the chopper wheel 34 were to stop rotating for any reason. Upon such an occurrence, the reset pulse would not be generated. The source generator 26 is designed to turn off if the reset pulse is absent for more than a few seconds in order to protect the filters A-F.

As indicated above, the band widths for the three gases CO, CH4, and C2H2 permit detection by a single detector assembly 28. The detector assembly 28 preferably comprises a lead-selenium (PbSe) detector having a suitable band width for the three gas channels. The lead-selenium detector is indicated at 48 in FIG. 1. The normal operating temperature for the detector 48 is approximately - 20o centigrade. This temperature is preferably maintained for example by means of a small semi-conductor type cooler unit built into the detector mounting 50. The cooling unit receives power from the instrument power supply through a conventional thermistor controlled temperature regulating circuit (not shown). An ellipsoidal radiation collector 52 is mounted around the detector 48 and assists the detector 48 in detecting a large fraction of the IR radiation which

is transmitted through the sample cell 18.

In addition, the sample cell 18 includes a number of additional features to enhance operation of the pulmonary function analyzer. For example, the internal volume of the sample cell 18 and the conduits 20 and 22 is limited as much as possible in order to increase the response time for the analyzer.

At the same time, it is noted that operating parameters for the infrared source 26 and the detector assembly 28 may be accurately calibrated to accommodate either turbulent or laminar flow conditions within the sample cell 18. However, in normal use turbulent flow is expected to be encountered under all normally rapid exhalations. It is also generally desirable that the subject exhale rapidly during use of the pulmonary function analyzer in order to avoid abnormal patterns of air flow from the lungs and to provide a reproducible air flow pattern. Accordingly, the design of the sample cell 18 is preferably configured for the purpose of inducing turbulent flow conditions therein at all times to permit constant calibrations for the detector 28. For this reason, the sample cell 18 is formed as a truncated pyramidal section with the conduit 20 being interconnected with the smaller end thereof. At the same time, the conduit 20 is arranged at an angle of approximately 60o to 75o relative to the center-line of the sample cell 18. The conduit 22 is arranged generally parallel with the conduit 20 as are the windows 30 and 32. With such an arrangement, exhalation flow from the conduit 20 tends to rapidly fill the sample cell 18 and induce turbulent flow conditions at the same time. Thus, the design of the sample cell along with the conduits 20 and 22 is selected both for the purpose of increasing the response time of the pulmonary function analyzer as well as making it more uniformly responsive to concentrations of the selected gases within the sample cell 18.

It was also noted above that it is additionally necessary to closely monitor the volume of flow through the sample cell 18 both during inhalation and exhalation in order to accurately determine alveolar volume. Within the embodiment of FIG. 1, the flow measurement is accomplished by measurement of a pressure drop induced by the above-noted configuration of the sample cell and the conduits 20 and 22. Because of the arrangement of these components as noted above, a pressure drop is developed between the conduits 20 and 22 which is measured by a pressure differential transducer having side arms 56 and 58 interconnected with the respective conduits 20 and 22. In order to provide a signal corresponding to flow volume through the sample cell 18, the transducer 54 is interconnected with a logarithmic function analyzer 60 for generating an analog signal proportional to flow volume through the cell 18. The analyzer 60 is in turn connected with an electronic integrator 62 which integrates the flow analog signal over a period of time for either inhalation or exhalation in order to provide an indication of inhaled or exhaled volume. Although this is a preferred means for measuring flow other means such as a pneumotach could also be employed along one of the conduits 20 or 22.

Accordingly, the optics unit 12 of FIG. 1 is effective to sequentially provide pulse signals corresponding to alignment of the filters A-F between the infrared source 26 and the detector assembly 28. Further, the optics unit 12 supplies a signal from the integrator 62 which corresponds to flow volume through the sample cell 18. These signals are delivered to the electronic processing unit 14 of FIG. 3 which, as noted above, includes generally conventional processing circuits for analyzing signals received from the optics

unit and providing a suitable display thereof.
Electronic Processing Unit (FIG. 3)

Referring now to FIG. 3, a block diagram of the electronic processing unit 14 is illustrated along with a schematic representation of various components described above for the optics unit 12. As was indicated above, the optics unit 12 and electronic processing unit 14 are constructed separately in order to facilitate use during pulmonary testing and to permit access to the optics unit for example to clean the sample cell.

Various electrical components contained within the optics unit or head include the infrared source 26, the drive motor 36 for the chopper wheel, the detector assembly 28 and a sample cell temperature regulator generally indicated at 64 in FIG. 3 for maintaining the temperature of the sample cell at approximately body temperature in order to avoid fogging within the sample cell and to also avoid undesirable effects of temperature variation during monitoring of the selected gases. In accordance with normal practice, a signal preamplifier 66 is mounted close to the detector assembly 28 in order to minimize noise pick-up, the preamplifier serving to communicate output pulses from the detector assembly 28 to the electronic processing unit 14.

Various electrical components for regulating operation of components within the optics unit include special regulators for controlling the detector bias and the thermal electric cooler for the detector (see FIG. 3). Also, the electronics unit includes conventional DC power supplies, regulator means for the infrared source 26 and decoder and pulse generator means for generating the synchronous gate pulses from signals received from the optical pick-up 38. As described above, the optical pick-up 38 itself is mounted adjacent the rim of the chopper wheel 34 in the optics unit.

As for the electronic processing unit 14, it is noted that numerous circuit arrangements may be employed in order to receive the electrical data described above from the optics unit 12 and to process it for analysis by an operator. FIG. 3 illustrates one combination of circuitry capable of performing this function.

As will be apparent from the preceding description, the signal emerging from the preamplifier 66 consists of a train of five pulses associated with the filters B-F followed by a space corresponding to the filter A where no signal exists.

This signal arrangement from the preamplifier 66 is first communicated to a common DC restorer 68. The above-noted space or pulse associated with the filter A is used as a gate to restore the DC base line within the restorer 68, thereby permitting the remainder of the electronic processing unit 14 to measure absolute signal amplitudes for the pulses received from the optics unit in connection with the other filters B-F.

Beyond the restorer 68, the electronic unit 14 includes a series of branched circuits for analyzing each of the gases monitored in the sample cell along with an additional similar branched circuit for receiving a circuit corresponding to water vapor in the sample cell. These branched circuits are referred to respectively at 70, 72, and 74 and 76 and relate respectively to signals for the gases methane, carbon monoxide, acetylene and water vapor. Each of the branched

circuits 70-76 includes similar components except for the signals to which each of the branched circuits is responsive. Those signals are indicated by capital letters corresponding to pulses received for the individual filters described above in conjunction with FIGS. 1, 2 and 2a.

Each analysis of pulmonary function is commenced with initiation of auto-zero cycle with zero gas in the sample cell 18, the cycle causing an auto-zero feedback loop in each of the circuits of channels 70-76 to add to or substract from the span reference pulse until the DC output is zero. Each feedback loop consists of a sample-and-hold circuit 78 and a zero multiplier 80. During the abovenoted cycle the negative feedback loop seeks a null in the output of the divider 84, developing a correction voltage which is sorted in the sample-and-hold circuit 78 for each channel or circuit 70-76 and is applied as a correction until a subsequent sample-and-hold cycle is initiated. As noted above, such a subsequent sample-and-hold cycle is initiated upon recommencement of the pulmonary function analysis either for the same subject or for a different subject.

As indicated in FIG. 3, each zero multiplier 80 is responsive to the pulses from the filters A and D. During operation of the pulmonary function analyzer in the analysis mode following the auto-zero cycle, the multiplier 80 responds to the sample-and-hold circuit 78 to correct the signal received from the DC restorer 68.

This correction factor is applied to a demodulator which is again responsive to both the span reference signal from the filter D and to the methane signal from the filter B. The demodulator is indicated in each of the branched circuits or channels 70-76 at 82. Signal and reference outputs from the demodulator 82 are applied to the divider circuit 84 which ratios the methane signal from filter B to the span reference signal from filter D in order to provide an output signal corresponding to methane sensed in the sample cell 18 (see FIG. 1). That output signal is in turn applied to a linearizing amplifier 86 which thus modifies the signal monitored through filter B in accordance with the physical law of absorption of radiation related to the concentration of methane in the sample cell. The other circuits 72, 74, and 76 similarly function to provide a corrected output signal indicative of the presence of carbon monoxide, acetylene and water vapor respectively within the sample cell. The output from the final circuit 76 for water vapor is applied through summing means 88 in order to accomplish the above-noted function of correcting the signal outputs for the circuits 70, 72, and 74 to minimize sensitivity thereof to water vapor in the sample cell.

Accordingly, there has been described a novel pulmonary function analyzer providing a rapid response for simultaneously monitoring two or more gases relating to different pulmonary functions. It will be obvious that numerous changes and modifications may be made in addition to those described above. Accordingly, the scope of the present invention is defined only by the following appended claims.

CLAIMS: What is claimed is:

[*1] 1. A method for non-invasively and continuously monitoring the three different pulmonary functions of alveolar volume, pulmonary diffusing capacity and pulmonary blood flow, comprising the steps of

providing a known volume of a gas including known concentrations of first, second and third selected gases for inhalation by a subject,

selecting the first gas as an inert gas having a measurable infrared absorption band,

selecting the second gas to also have a measurable infrared absorption band and a relatively high affinity for hemoglobin with a measurable rate of absorption or diffusion through alveolar capillary walls in order to monitor the function of pulmonary diffusing capacity,

selecting the third gas to also have a measurable infrared absorption band, the third gas also being selected to readily diffuse through alveolar capillary surfaces or walls of the lungs while having a measurable degree of solubility in blood in order to monitor the pulmonary function of capillary blood flow,

causing the subject to inhale said first, second and third gases,

thereafter passing expiration gases from the subject through a sample cell,

simultaneously detecting the concentrations of said first, second and third gases in said sample cell by directing infrared radiation through said sample cell and detecting the amount of absorption due to each of said first, second and third gases, and

measuring the volume of gas exhaled by the subject in order to determine alveolar volume by means of the detected first gas concentration while simultaneously monitoring the pulmonary functions of diffusing capacity and capillary blood flow by means of the detected second and third gas concentrations.

[*2] 2. The method of claim 1 wherein said first, second and third gases are further selected to have infrared absorption bands which are relatively distinct from each other and from interferent gases normally found in the lungs.

[*3] 3. The method of claim 2 wherein said first gas is methane, said second gas is carbon monoxide and said third gas is acetylene.

[*4] 4. A method for analyzing different pulmonary functions including alveolar volume and a second pulmonary function, comprising the steps of

providing a known volume of gas with known concentrations of first and second selected gases for inhalation by a subject;

selecting the first gas as an inert gas having a measurable infrared absorption band,

selecting the second gas to also have a measurable infrared absorption band, the second gas also being effective to provide an indication of a second pulmonary function,

causing a subject to inhale the first and second gases,

thereafter passing expiration gases from the subject through a sample cell,

simultaneously detecting the concentrations of said first and second gases in said sample cell by directing infrared radiation through said sample cell and detecting the amount of absorption due to said first and second gases, and

measuring the volume of gas exhaled by the subject in order to simultaneously determine alveolar volume by means of the first gas detected concentration and monitor said second pulmonary function by means of the detected second gas concentration.

[*5] 5. The method of claim 4 wherein said second gas is selected to have relatively high affinity for hemoglobin and a measurable rate of absorption or diffusion through alveolar capillary walls in order to monitor the pulmonary function of diffusing capacity thereby.

[*6] 6. The method of claim 5 wherein said first gas is methane and said second gas is carbon monoxide.

[*7] 7. The method of claim 4 wherein said second gas readily diffuses through alveolar capillary surfaces or walls of the lungs while having a measurable degree of solubility in blood in order to monitor the pulmonary function of capillary blood flow.

[*8] 8. The method of claim 7 wherein said first gas is methane and said second gas is acetylene.

[*9] 9. The method of claim 4 further comprising the steps of simultaneously monitoring the concentration of water vapor within the sample cell by detecting the amount of infrared absorption thereby in order to correct any error in the measurement of said first and second gases because of interference due to said water vapor.

[*10] 10. The method of claim 4 further comprising the steps of also directing the infrared radiation through an enclosed quantity of an interferent gas prior to the detection of infrared absorption, the interferent gas being selected as a gas capable of appearing in the sample cell and interfering with the proper detection of said first and second gases.

[*11] 11. The method of claim 10 wherein said interferent gas is carbon dioxide.

[*12] 12. The method of claim 11 wherein said first gas is methane and said second gas is carbon monoxide.

[*13] 13. The method of claim 4 further comprising the steps of selecting a third gas to have a measurable infrared absorption band relatively distinct from the absorption bands for said first and second gases, causing the subject to inhale said third gas along with said first and second gases, simultaneously detecting the concentration of said third gas along with the concentrations of said first and second gases in said sample cell, and monitoring a third pulmonary function by means of the detected third gas concentration simultaneously with the determination of alveolar volume by means of the

detected first gas concentration and the monitoring of said second pulmonary function by means of the detected second gas concentration.

[*14] 14. The method of claim 13 wherein said second gas is selected to have relatively high affinity for hemoglobin and a measurable rate of absorption or diffusion through alveolar capillary walls in order to monitor the pulmonary function of diffusing capacity, said third gas being selected to readily diffuse through alveolar capillary surfaces or walls of the lungs while having a measurable degree of solubility in blood in order to monitor the pulmonary function of capillary blood flow.

[*15] 15. The method of claim 14 wherein said first gas is methane, said second gas is carbon monoxide and said third gas is acetylene.

[*16] 16. The method of claim 14 comprising the additional step of also detecting the concentration of water vapor in the sample cell and correcting errors in the measurement of said first, second and third gases due to interference from water vapor.

[*17] 17. A pulmonary function analyzer for simultaneously and continuously monitoring the three pulmonary functions of alveolar volume, pulmonary diffusing capacity and pulmonary blood flow comprising

a source containing first, second and third selected gases, said source including means for permitting inhalation into a subject's lungs of a known composite gas volume including known concentrations of the first, second and third selected gases, the first gas being an inert gas having a measurable infrared absorption band, the second gas having a measurable infrared absorption band and a relatively high affinity for hemoglobin with a measurable rate of absorption or diffusion through alveolar capillary walls in order to monitor the function of pulmonary diffusing capacity, the third gas also having a measurable infrared absorption band, the third gas also being readily diffusible through alveolar capillary surfaces or walls of the lungs while having a measurable degree of solubility in blood in order to monitor the pulmonary function of capillary blood flow,

a sample cell including an infrared source of radiation and an infrared detector means arranged at opposite ends thereof to continuously monitor the concentrations of said gases within said sample cell,

inlet means for permitting flow of said gases exhaled by the subject into said sample cell,

outlet means for allowing said flow of gases to exit frsaid sample cell,

means for measuring the composite gas volume exhaled by the subject through said sample cell, and

means responsive to said infrared detector means and responsive to said means for measuring composite gas volume for simultaneously monitoring alveolar volume, pulmonary diffusing capacity and pulmonary blood flow.

[*18] 18. The pulmonary function analyzer of claim 17 wherein said inlet means comprises a conduit including a mouthpiece, said outlet means including a

conduit for connecting the sample cell with an exhaust means to permit the monitoring of gases being passed through the sample cell from the mouthpiece toward the exhaust means.

[*19] 19. The pulmonary function analyzer of claim 18 further comprising means for alternately connecting said conduit of said outlet means with said source so that said selected gases may pass through said sample cell toward the mouthpiece during inhalation while continuously monitoring the concentrations of said gases during both inhalation and expiration.

[*20] 20. The pulmonary function analyzer of claim 19 further comprising electronic processing means for processing signals passing from said infrared detector means in order to continuously and instantaneously monitor the concentrations of selected gases in said gas flow through said sample cell during both inhalation and expiration.

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5,042,501

<=2> GET 1st DRAWING SHEET OF 4

Aug. 27, 1991

Apparatus and method for analysis of expired breath

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SEARCH-FLD: 128#716, 719, 725, 730

REF-CITED:

U.S. PATENT DOCUMENTS

4,485,822	12/1984	* O'Conner et al.	128#719
4,850,371	7/1989	* Broadhurst et al.	128#719

FOREIGN PATENT DOCUMENTS

0153741	9/1985	* European Patent Organization	128#719

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ABST:
Apparatus and method for providing breath for introduction to a measuring device such as a mass spectrometer. The apparatus includes a mouthpiece for interfacing a subject with the apparatus; a tube for carrying exhaled breath from the subject to the inlet of a mixing chamber; a mixing chamber having an inlet, sample outlet and exit tube, that provides a residence time for the exhaled breath sufficient to mix the breath and provide an adequate sample to the measuring device; and heating apparatus for maintaining the apparatus above a temperature where condensation of vapor occurs.

NO-OF-CLAIMS: 18
EXMPL-CLAIM: <=5> 1

NO-OF-FIGURES: 5

NO-DRWNG-PP: 4

SUM:

FIELD OF THE INVENTION

The invention serves as an interface between a subject (human or animal) and a measuring device. The invention differs from prior art in that whole (i.e. undiluted) breath is analyzed in a realtime continuous manner. No preanalysis collection or concentration is needed, and rapid response is achieved. No subject intervention is needed to control the introduction of breath except to breathe normally. In one embodiment of the invention for analysis of human breath, a 3 liter mixing chamber is continuously purged by breath; by sampling from this chamber at a constant flow rate a continuous realtime analysis of breath can be performed for clinical toxicology, occupational medicine and exercise physiology studies.

BACKGROUND OF THE INVENTION

The assessment of individual personal exposure to toxic substances is an important component of human and animal health risk assessment. Assessment of exposure by the analysis of breath is particularly attractive since it is noninvasive and nontraumatic for the subject. Breath may also be a less complex medium than blood or urine, and so may be easier to analyze and characterize. For these reasons, breath analysis has been applied in several studies addressing exposure to toxic chemicals, or investigating natural metabolites such as indicators of disease, see for example: A. Zlatkis, R. Brazell, and C. Poole, Clin. Chem., 27, 289-297, 1981; B. Krotoszyinski, G. Gabriel, and H. J. O'Neill, Chrom. Sci., 15, 239, 1977; S. Chen, L. Zieve, and V. Mahadevan, J. Lab. Clin. Med., 75, 628-635, 1970; M. Simenhoff, J. Burke, J. Saukkonen, A Ordinavio, and R. Doty, New England J. Med., 297, 132-135, 1977; B. Lorber, Amer. Rev. Resp. Dis., 112, 875-877, 1975; F. Brugnone, L. Perbellini, P. Apostoli, and E. Gaffuri, "Monitoring of Industrial Exposure to Organic Volatile Compounds by Analysis of Alveolar Air and Blood", American Chemical Society 187th National Meeting, St. Louis, Mo., 1985; M. Hisamura, Nippon Naika Gakkai Zasshi, 68, 1284-1292, 1979; A. Tangerman, M. T. Meuwese-Arends, J. H. M. van Tongeren, J. Lab Clin. Med., 106, 175-182, 1985; L. Campbell, D. M. Marsh, and H. K. Wilson, Ann Occup. Hyg., 31, 121-133, 1987; R. W. Handy, H. L. Crist, T. W. Stanley, "Quality Assurance For Personal Exposure Monitoring", in Quality Assurance For Environmental Measurements, ASTM Special Technical Publication No. 867, 284-296, 1985; and A. W. Jones, G. Maardh, E. Aenggard, Pharmoacol. Biochem. Behav., 18, 267-272, 1983. In most of the studies breath analysis has been performed by integrated collection of breath in bags, on sorbent materials, or in cryogenic traps. Such approaches may suffer from poor time resolution, inefficient sample collection or recovery, or sample degradation.

Further, breath analysis is useful in the study of natural metabolites, including indicators of disease, as well as bodily effects due to exposure to toxic chemicals. By monitoring whole breath continuously, in realtime, many studies in chemical toxicology, occupational medicine and exercise physiology

can be performed.

Recently attempts have been made to apply the considerable sensitivity and selectivity of tandem mass spectrometry (MS/MS) to breath analysis, by employing atmospheric pressure chemical ionization (APCI) as the ionization source, see for example: A. M. Lovett, N. M. Reid, J. A. Buckley, J. B. French, and D. M. Cameron, Biomed. Mass Spectrom., 6, 91-97, 1979 F. M. Benoit, W. R. Davidson, A. M Lovett, S. Nacson, and A. Ngo, Anal. Chem., 55, 805-807, 1983; and F. M. Benoit, W. R. Davidson, A. M. Lovett, S. Nacson, and A. Ngo, Int. Arch. Occup. Environ. Health, 55, 113-120, 1985. However, such efforts have been limited by the means used to introduce breath into the mass spectrometer. The breath inlets used required the subject to control his breath flow rate or an observed pressure gauge reading during exhalation, required dilution of breath with a continuous flow of clean air, and provided only intermittent data (i.e., during each exhalation).

Other relevant art known to the inventors includes the following U.S. Pat. No.: *4,772,559* to Preti et al. discloses a method of detecting and diagnosing an individual to determine the presence of bronchiotic carcinoma by analysis of expired lung air; U.S. Pat. No. *4,485,822* to O'Connor et al. relates to a system and method for interfacing a patient with equipment for monitoring gaseous components of the exhalation of the patient and emphasizes the elimination of dead space volume and a disc filter for removing secretions and humidification; U.S. Pat. No. *4,178,919* to Hall reveals a flowmeter for providing synchronized flow data and respiratory gas samples to a medical mass spectrometer; U.S. Pat. No. *4,167,667* to Fletcher, et al. discloses a respiratory gas moisture separator system for mass spectrometer monitoring systems that relies on a pressure drop to maintain moisture in the vapor state and a momentum separator to remove water droplets; U.S. Pat. No. *3,759,249* to Fletcher, et al. relates to a method and apparatus for obtaining an analysis of respiratory gas flow rate and frequency of inspiration and expiration cycles on a "real time" basis; U.S. Pat. No. *3,649,199* to Littlejohn reveals a method for detecting trace quantities of an organic drug material in a living animal and relies on a membrane gas separator for direct breath analysis (column 3, lines 29-32); U.S. Pat. No. *3,622,278* to Etzinga discloses a method and means for measuring and analyzing the composition of alveolar air for determining the volatile constituents in blood. The device eliminates air from the dead air spaces of the respiratory tract thereby avoiding dilution of alveolar air.

An object of the present invention is to provide an improved breath interface which allows continuous analysis of undiluted breath by APCI/MS/MS. A further object is to provide an improved breath interface that reduces the loss of trace constituents in breath to a minimum. A still further object is to provide an improved breath interface that is easy to use and reliable.

BRIEF DESCRIPTION OF THE INVENTION

A breath interface apparatus provides breath for introduction to a measuring device. It consists of subject interface means for interfacing the subject with the apparatus; tube means for carrying exhaled breath from the subject interface means to the inlet of a mixing chamber; a mixing chamber having an inlet, sample outlet and exit tube means, that provides a residence time for the exhaled breath sufficient to mix the breath and provide a sufficient sample to the measuring device; and heating means for maintaining the apparatus above a temperature where condensation of vapor occurs.

A method for measuring trace constituents in a subject's breath encompasses providing a subject interface means to obtain breath from the subject; flowing breath obtained from the subject to a mixing chamber; mixing the breath in the mixing chamber; flowing breath samples from the mixing chamber to a measuring device and exiting unneeded breath from the mixing chamber; and maintaining the breath above the condensation temperature of vapor in the breath and preventing condensation on the apparatus by heating.

DRWDESC:
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a semischematic drawing illustrating details of the apparatus of the invention.

FIG. 2 is a semischematic drawing depicting exemplary components of a TAGA (Registered Trademark) instrument useful with the invention.

FIG. 3 is a semischematic drawing illustrating details of the apparatus when used with a TAGA instrument as the measuring device.

FIG. 4 is a drawing of details of a narrow bore inlet tube that is preferred when using the apparatus with a TAGA instrument.

FIG. 5 is a graph illustrating the response of a TAGA spectrometer to lactic acid in breath and from a control when used with the apparatus of the invention.

DETDESC:

DETAILED DESCRIPTION OF THE INVENTION

In general, the apparatus of the invention functions as an interface between a subject and a measuring device. In a preferred embodiment of the invention the apparatus acts as an interface between a subject and a mass spectrometer.

The breath interface 100 is shown in FIG. 1 for providing exhaled breath. A subject uses a conventional mouthpiece 110 (subject interface means) and breathes normally. One way breathing valves 111,112 (e.g. Hans Rudolph Model 2600) are arranged in relation to the mouthpiece 110 so that exhaled breath 115 is pushed into the inlet 116 while inhaled air 113 can be drawn from the room, from sources of clean air, or from prepared gas mixtures (not shown). By this means, the air supplied to the subject can be controlled without hindering the exhalation mechanism. Alternatively, other apparatus (having the function of a mouthpiece e.g. tracheotomy tube) known in the art for interfacing with a subject may be used to obtain a breath sample 115 from the subject. The breath sample 115 is then transported through a large diameter tube 120 (preferably flexible and of Teflon), to inlet tube 130 and past gas inlet ports 131, and into a mixing chamber 140. The entire flow system from the mouthpiece 110 to the measuring device 200 is heated by heating means 170 to prevent condensation of exhaled water vapor and minimize surface losses of trace substances in the breath sample. The heated portion is depicted by the shaded area in FIGS. 1 and 3. If desired, the mouthpiece (subject interface means) 110 may also be heated. The gas inlet ports 131 may be used to flush the system with zero air, add gaseous standards, or allow the withdrawal of sample for other tests. The breath

sample is drawn into the measurement device 200 through sample outlet tube 150. Excess exhaled air 115 is vented at a large bore exit tube 160. Inlet tube 130 and exit tube 160 preferably extend into the mixing chamber 140 and preferably have bent portions 130A,160A respectively that are oriented in opposite directions to promote mixing of the continuous breath sample. Alternatively, baffles (not shown) could be used at the inlet and exit tubes 130,160 as is known in the art to promote mixing. Mixing chamber 140 may be of glass, stainless steel, nickel, Teflon or similar material or other materials lined with these. Connectors and adaptors may be of similar materials. If desired the mixing chamber may be of flexible materials or have movable walls (not shown) to allow adjustment in volume.

The size of the mixing chamber can be adjusted to obtain a residence time of about 1 to 60 seconds. At high breath rates the residence time can be very short whereas at low rates longer residence times are required to achieve an integrated sample. Flow rates and size of the mixing chamber are related to the breath rate provided by the subject. For example, if the subject tested is a small animal having a low breath rate (e.g. dog, cat, mouse) the mixing chamber and flow rate are scaled down to provide proper residence times and sample flow rates. Sample flow to the TAGA must be adjusted to be lower than the lowest flow of breath from the subject to preserve sample integrity. Exhaust vacuum at sample outlet 212 can be adjusted to accommodate high or low flow rates. Flow rates may be as low as about 0.1 liters/minute and as high as about 100 liters/minute.

Heating means 170 uses preferably resistance wire heating and associated control means where the heating wires are wound around or placed over the surfaces to be heated. Additionally, insulation (not shown) may be used in conjunction with heating means 170 if needed or desired for better control. It is the use of heating means 170 that provides the desired reduction in the loss of trace constituents of sampled breath by preventing condensation of vapor.

Exhaled breath is normally saturated with water vapor (100 per cent relative humidity). The exhaled breath is also normally at or very near body temperature. For humans this temperature is about 37 C. (98.6 F.), but will vary for each subject. Thus, the heating means must maintain all parts of the apparatus in contact with expired breath above the temperature where condensation would occur. These temperature relationships can easily be determined by those skilled in the art. It is preferred that a temperature slightly higher than the subjects body temperature be used.

The prevention of condensation is important since any condensate will remove trace components from the sampled breath and give false readings. Of similar importance is the need to provide materials or lining for the tubing, connectors, mixing chamber, etc. that will not absorb, adsorb or otherwise react with breath components.

The measuring device 200 used in the examples below was a TAGA mass spectrometer 201 (Model 6000E), an atmospheric pressure chemical ionization (APCI) tandem mass spectrometer. It is a sensitive, specific, fast, and versatile analyzer for air analysis. Components of the TAGA 201 are illustrated in FIG. 2. The basic components are the inlet module 210, ionization source 220, transfer ion lenses 230, three quadruple mass filters 241, 242, 243, and the detector 250. Samples of air streams are introduced at sample inlet 211 and

exhausted at sample exhaust 212. Trace contaminants in the sampled air stream are ionized by a corona discharge 214 at atmospheric pressure. Ionized molecules
are electrically accelerated through a counter current flow of dry nitrogen 215 toward a small orifice 216 where they are carried into a cryogenic vacuum system 217 by a small flow of nitrogen gas. The ion transfer lenses 231 eliminate the majority of the nitrogen gas while electrically focusing the ions into the first quadruple mass analyzer 241. The first quadruple 241 typically functions as a mass filter by eliminating all but those ions of a specific mass of interest. The mass of interest is selected to correspond to a molecular ion of a particular contaminant which may also include molecular or fragment ions of interfering species. Ions passing through the first quadruple 241 are accelerated into the second quadruple 242 where they are intercepted by a neutral beam of argon 219 or other inert gas atoms. Collision with argon atoms at region 221 results in fragmentation of the ions in a predictable manner characteristic of their molecular structure. Fragments resulting from the molecular ion of interest are then sorted out from fragments of interfering ions by the third quadruple 243 mass analyzer. As a result of the tandem mass analyzers, the TAGA achieves a highly specific measurement for a given combination of mass analyzer settings. The TAGA can monitor several specific target compounds simultaneously or can scan a mass range for compounds which have a common structural feature. Conventional scanning modes provide information for the identification of unknowns.

When a TAGA spectrometer 201 is used for example with a human subject, samples are removed from the mixing chamber 140 by way of outlet tube 150 at a constant flow of about 3 L/min. This is greatly reduced from the typical TAGA flow of 30-100 L/min used in atmospheric sampling.

Referring to FIG. 3, an adaptor 310 provides for connection to outlet tube 150, the sample inlet tube 400 to the TAGA, and vaporizer probe 320 with unions 311,312 and cap 313. The original sample inlet tube to the TAGA is replaced by a narrow bore sample inlet tube 400 which enhances sensitivity in breath analysis by more efficiently directing sample flow into the ionization region 214. The liquid vaporizer probe 320 is supplied by an external calibration source, a syringe drive 330 is depicted, that delivers calibration solutions into the TAGA sample flow that flows from tube 150 through connector 310 to sample inlet tube 400, allowing standard additions to the breath sample without interrupting analysis. In the examples herein aqueous lactic acid solutions of 10 < - 4> M were used for calibration. A human adult subject even at rest can easily supply more than the 3 L/min flow required by the TAGA as configured in the preferred embodiment for human subjects as described herein; the large bore exit tube 160 allows excess breath to be diverted with negligible flow restriction. This exit tube 160 can also be used to supply breath for other tests.

The apparatus and method may be adapted to other mass spectrometers by controlling the flow of sample gases. For example, with the TAGA it does not matter if water vapor is in the sample. With other mass spectrometers this may be a problem and the water vapor will have to be removed. This will not work as well since trace species will be removed with the water.

FIG. 4 provides details of the inlet tube 400. The inlet tube 400 is secured to the system by a threaded connection 401 that provides support and seals the TAGA 201 and adaptor 310 with union 312. The inlet tube comprises an inner tube

403 and outer tube 404. The inner tube 403 is sealed at one end 405 to outer tube 404 while Teflon ring 402 provides for support between tubes 403,404 at their other ends and seals the space 406 between them. The diameter of the bore 407 in tube 403 is reduced to 6 mm from that of the inlet tube normally used in the TAGA 201. This reduction in the tube size provides improved transport of the breath flow into the ionizing region 214 of the TAGA 201, resulting in a sensitivity about five (5) times higher than that obtained with the larger tube. Nonionized sample then exits the TAGA through outlet 212 to a pump (not shown). Ions from the sample proceed to detection as described above. The inner tube 403 is heated by heating tape or similar auxiliary heating means 408 that is connected to heating means 170 by connector 409.

The diameter of bore 407 may be further adjusted to accommodate lower flows other than those used with the human subjects described herein. Small mammals, for example, would require much smaller bores to improve sensitivity by improved transfer of sample into the ionization region 214. These can easily be determined by those skilled in the art having read the teachings herein.

The breath interface 100 has undergone a variety of tests. Heating of the breath flow path prevents condensation of breath moisture at breath flow rates from 5 to over 100 L/min, characteristic of subject activity levels ranging from rest to vigorous exertion. Calibrations have been performed using several different procedures in addition to the normal mode of calibration described above. The additional calibration tests have shown the same results when the calibration probe is positioned upstream of the breath interface 100 as when it is positioned in the normal downstream position (see FIG. 3). These tests have also shown no effect of flow rate in the breath interface 100 on TAGA response. Further tests using humidified air have disclosed no transient effects due to the introduction of humidity into the inlet, as occurs at the onset of breathing into the device. However, these tests and calibration procedures have shown that TAGA sensitivity to lactic acid in breath or in air with 100 percent humidity is reduced by about 30 percent relative to that in dry air. This finding indicates the need to calibrate by standard addition to the breath matrix, a capability which is built into the apparatus described herein.

As an example for detection of trace substances in breath, lactic acid has been monitored continuously in breath over time periods from a few minutes up to nearly an hour, during exercising of a human subject on a stationary bicycle. FIG. 5 shows an example of monitoring lactate in breath during a brief exercise period (time (t) in minutes on the x axis and intensity (I) in ion counts per second on the y axis). Lactic acid is detected by monitoring of daughter ions of masses 45 (solid line) and 43 (dotted line) arising from the fragmentation of lactate anion (mass 89). The graph shows the following periods as noted at the bottom thereof:

A. background, zero air

B. subject started breathing into inlet

C. 8.2 ppb standard addition with syringe drive introduction of lactic acid

D. subjects breath only, syringe drive off

E. zero air flush of system.

The subject began breathing into the mouthpiece 110 at rest, and after a short time began exercising on a stationary bicycle, continuing for several minutes until moderate exertion and resulting increased breath rate were reached. While the subject was exercising, lactic acid response was calibrated by standard addition to the breath flow. Then the subject stopped exercising, and finally the system was flushed with clean purified air. Response to the breath concentration of lactic acid was seen within five seconds once the subject started breathing into the system. An approximately steady state was quickly established with no evidence of variation of signal due to the breathing cycle.

Also of interest in FIG. 5 are data from the end of the experiment. Region E shows a sharp decline in signal when the system is flushed with clean air and breath analysis ends. The lactic acid signal in zero air drops rapidly to that seen before the breath analysis, indicating little memory effect in the breath interface 100.

A standard addition of lactic acid to the breath flow is superimposed upon the breath lactate signal in FIG. 5; the spike at the start of calibration is due to instability in the syringe drive/vaporizer system when first turned on. Lactate concentrations in breath shown in FIG. 5 and observed in other tests are a few ppbv, consistent with calculations based on the pKa and Henry's law constant for lactic acid, roughly millimolar concentrations of lactate in blood, and a pH for body fluids of about 7. Acetic and pyruvic acids were also monitored in some tests, and were present at concentrations well below those of lactic acid. The continuous and stable response shown in FIG. 5, which contrasts with the results of the prior art employing APCI/MS/MS in which measurements were made only on individual exhalations. The lactate concentration in whole breath was generally observed to remain constant or to decrease during the exercise tests as breathing rate increased. However, calculations incorporating breath flow rate indicate that the total output of lactate in breath increased greatly during exercise, parallel to the power output of the subject. The amounts of lactic acid excreted in breath are negligibly small compared to the total amount of lactic acid in other reservoirs within the body; however, these tests on breath lactate serve to illustrate the use of the device in breath analysis for industrial hygiene tests, hazardous material exposure studies, bioresponse tests, pharmaceutical kinetic studies, and disease detection. For example, workers in a chemical plant would be monitored for chemicals they were exposed to such as organic solvents (benzene, toluene and the like); human or animal subjects would be monitored to determine metabolism of foods (e.g. breath fresheners, artificial sweeteners); human or animal subjects would be monitored for the metabolism of drugs in the body versus time (e.g. anesthetics); subjects would be monitored for detection of compounds indicative of disease (e.g. sulfur compounds in liver disfunction), or to determine levels of various compounds such as ammonia or acetone indicative of various body states, and so on.

The breath interface 100 requires no attention from the subject, and thus is applicable to subject activity ranging from rest to extreme exercise for a great latitude in breathing rates. The apparatus is useful for the flow rates indicated above.

While the forms of the invention herein disclosed constitute presently preferred embodiments, many others are possible. It is not intended herein to

mention all of the possible equivalent forms or ramifications of the invention. It is to be understood that the terms used herein are merely descriptive rather than limiting, and that various changes may be made without departing from the spirit or scope of the invention.

CLAIMS: We claim:

[*1] 1. An apparatus for providing breath from a subject for introduction to a measuring device comprising:

a. subject interface means for interfacing the subject with the apparatus;

b. tube means for carrying exhaled breath from the subject interface means to the inlet of a mixing chamber;

c. a mixing chamber having an inlet, sample outlet and exit tube means, that provides a residence time for the exhaled breath sufficient to mix the breath and provide a sufficient sample to the measuring device; and

d. heating means for maintaining b. and c. above a temperature where condensation of vapor occurs.

[*2] 2. The apparatus of claim 1 comprising:

e. adaptor means for introducing sample breath from the mixing chamber to a measuring device; and

f. additional heating means for maintaining the adaptor means above a temperature where condensation occurs.

[*3] 3. The apparatus of claim 1 wherein the heating means includes means for maintaining the subject interface above the temperature where condensation of vapor occurs.

[*4] 4. The apparatus of claim 1 wherein the subject interface means constitutes a mouthpiece or a tracheotomy tube.

[*5] 5. The apparatus of claim 1 wherein the tube means has means for connection to a mass spectrometer.

[*6] 6. The apparatus of claim 1 wherein the mixing chamber has movable walls for adjustment of volume.

[*7] 7. The apparatus of claim 1 wherein the heating means constitutes a resistance wire and associated control means.

[*8] 8. The apparatus of claim 1 wherein a calibration device is connected to the sample outlet to provide standards for the measuring device.

[*9] 9. The apparatus of claim 1 wherein the materials that constitute the breath interface apparatus are inert to the materials to be tested.

[*10] 10. A method for measuring trace components in a subject's breath comprising:

a. providing a subject interface means to obtain breath from the subject;

b. flowing breath obtained from the subject to a mixing chamber:

c. mixing the breath in the mixing chamber;

d. flowing breath samples from the mixing chamber to a measuring device and exiting unneeded breath from the mixing chamber; and

e. maintaining the breath in steps a, b, c, and d above the condensation temperature of vapor in the breath.

[*11] 11. The method of claim 10 whereby the residence time is maintained between about 1 second to about 60 seconds.

[*12] 12. The method of claim 11 whereby the residence time is maintained above about 30 seconds.

[*13] 13. The method of claim 10 whereby the providing step includes a mouthpiece or a tracheotomy tube as the subject interface.

[*14] 14. The method of claim 10 whereby the sample flow rate is maintained between about 0.1 liters per minute to about 100 liters per minute.

[*15] 15. The method of claim 14 whereby the sample flow rate is maintained above about 3 liters per minute.

[*16] 16. The method of claim 10 comprising:

f. providing a mass spectrometer as the measuring device.

[*17] 17. The method of claim 10, whereby the system is flushed with clean air between analysis.

[*18] 18. The method of claim 10 whereby a calibration standard is injected into the breath samples from the mixing chamber.

115TH PATENT of Focus printed in FULL format.

4,772,559

Sep. 20, 1988

Method of detecting the presence of bronchogenic carcinoma by analysis of expired lung air

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CL: 436;95;128;436;

SEARCH-FLD: 55#67; 128#716, 717, 719, 730; 436#64, 96, 111, 140, 161, 181, 813, 900

REF-CITED:

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ABST:
A novel method of detecting and diagnosing lung cancers by monitoring and analyzing expired lung air for the presence of selected aromatic amines, particularly aniline and ortho-toluidine, is provided.

NO-OF-CLAIMS: 10

EXMPL-CLAIM: <=9> 1

NO-OF-FIGURES: 0

NO-DRWNG-PP: 0

PARCASE:

This is a continuation, of application Ser. No. 786,378, filed Oct. 10, 1985, now abandoned.

SUM:

BACKGROUND OF THE INVENTION

The incidence of lung cancer in the United States is currently over 100,000 new cases per year and is expected to rise to nearly 300,000 by the year 2000. G. Gori and J. Peters, Prev. Med. 4:239-246 (1975). This expected increase is related both to the continued use of cigarettes and to exposure to various pollutants that exist in the work place and in urban home environments. More than two-thirds of the cases of bronchogenic carcinoma afflict middle-aged men, but the incidence among women is rising, and the proportion of female patients is expected to rise at an even greater rate as the effects of women's having entered the work place and begun smoking in increased numbers years ago are seen. The incidence today of lung cancer is 4-10 times greater in moderate cigarette smokers than in nonsmokers, and is 15-30 times greater in heavy smokers than in nonsmokers. The rising incidence is particularly alarming in view of the latent nature of this disease since the effect of exposure to a variety of substances found in industrial environments, such as asbestos, are just beginning to be seen.

Despite considerable efforts at early diagnosis and treatment, survival rates for bronchogenic carcinoma remain low. Although prognosis depends not only on cell type but also on the stage at which the disease is detected, the overall survival rate is still only about 10-25%. Recently, efforts have been made to more closely survey those individuals who fall into defined high-risk groups, such as those who smoke heavily or who are or have been chronically exposed to known carcinogens. Thus far, the most promising approach has been the screening of males of 45 years of age or older who have smoked at least 2 packs of cigarettes a day for 20 years. A combination of chest x-ray and pooled sputum analysis every four months has indicated lung cancers at an early stage of the disease, yielding a more favorable prognosis. More invasive methods of detecting

the disease have been made, such as the use of fiber optic bronchoscopy, but these approaches have not significantly affected the rate of early diagnosis, which is still thought to be one of the most important considerations to long-term survival or ultimate cure.

The detection of other disease states by non-invasive methods has, so far, out-paced the use of such methods to detect lung cancer. Lung air, breath, and saliva are, for example, easily obtainable physiological samples that contain an array of volatile constituents whose presence has provided evidence of other systemic disease conditions or infection. The chemical identity of many volatile constituents, as well as their use in the study and diagnosis of diabetes, respiratory virile infection, and renal insufficiency has been described. A. Zlatkis, R. Brazell and C. Poole, Clin. Chem., 27:789-797 (1981). Analysis of respiratory air by gas chromatography/mass spectrometry has shown the presence of simple endogenous alcohols, ketones, amines and numerous compounds of exogenous origin. B. Krotoszyinski, G. Gabriel and H. J. O'Neill, Chrom. Sci. 15:239 (1977). In several disease conditions, for example, specific volatile metabolites have been identified in breath samples, having been transferred into the aveolar air space from the blood. An example is the elevated levels of mercaptans and lower aliphatic acids found in the breath of patients with cirrhosis of the liver. S. Chen, V. Mahadevan and L. Zieve, J. Lab. Clin. Med, 75:622-27 (1970).

Monitoring the quantitative change in the presence of known indicators of disease or infection, over time, can indicate changes in physiological state, reflecting the advancement of the disease or the effect of treatment. For example, the classic uremic breath odor denotes the presence of dimethylamine and trimethylamine. M. Simenhoff, J. Burke, J. Saukkonen, A. Ordinario and R. Doty, New England J. Med., 297:132-135 (1977) Gas chromatography/mass spectrometry analysis of breath volatiles, however, shows a marked reduction in the concentration of these amines following hemodialysis, demonstrating the relationship between lung air and blood for small organics and the use of sampling lung air to monitor treatment efficacy.

The detection of various other pathological states through the analysis of volatiles given off by various body samples is documented. High concentrations of acetone in breath samples of diabetics has been found. A. Zlatkis, R. Brazell and C. Poole, Clin. Chem., 27:789-797 (1977). It has also been speculated that bacterial infections of the lung could be a further source of indicative volatiles present in expired lung air. B. Lorber, Amer. Rev. Respiratory Dis., 112:875-877 (1975). U.S. Pat. No. *4,349,626* (issued Sept. 14, 1982, to Labows et al) discloses a method of detecting the presence of Pseudomonas aeruginosa through the analysis of characteristic volatile metabolites, such as various ketones and/or sulfur metabolites, associated with this infection. The disclosed detection method involves analyzing the volatiles in a head space over a sample of material associated with the site of the suspected infection, such as skin, sputum, breath, or saliva. U.S. Pat. No. *4,334,540* (issued June 15, 1982 to Preti et al) discloses a method of diagnosing periodontal disease through the detection of pyridine compounds in the headspace over, for example, breath or saliva samples.

The application of gas chromatography analysis techniques to the identification of unknown microorganisms is well known in general, and as described above, has been used in detection of various organic metabolites. See

Zechman and Labows, "Volatiles of Pseudomonas aeruginosa and Related Species by Automated Headspace Concentration - Gas Chromatography," Can. J. Microbiol 31:232-237 (1985). The techniques which have been developed are based on analysis of either the unique metabolites of a given organism or on its individual structural components. Culture extracts have, for example, revealed specific amines for Clostridia (Brooks et al), "Further Studies on the Differentiation of Clostridium sordelli from Clostridium bifermentans by Gas Chromatography", Can. J. Microbiol., 16:1071-8 (1970). Specific hydroxy acids and fatty acids have been identified for Neisseria. Brooks et al, "Analysis by Gas Chromatography of Hydroxy Acids Produced by Several Species of Neisseria", Can. J. Microbiol. 18:157-168 (1972); Brooks et al, "Analysis by Gas Chromatography of Fatty Acids Found in Whole Cultural Extracts of Neisseria Species", Can. J. Microbiol. 17:531-541 (1970). As mentioned above, bacteria cell wall preparations have been examined for unique fatty acid profiles, including such profiles for Pseudomonads. C. W. Moss, S. D. Dees, "Cellular Fatty Acid and Metabolic Products of Psuedomonas Species Obtained from Clincal Specimens", J. Clin. Microbio., 4:492-502 (1976); and T. J. Wade, R. J. Mandel, "New Gas Chromatographic Characterization Procedure: Preliminary Studies on Some Pseudomonas Species", Applied Microbio., 27:303-311, (Feb. 1974). Pyrolysis-gas chromatography of whole cell Clostridia bacteria has also been reported as giving identifiable differences in the observed fragmentation patterns. Reiner, et al, "Botulism: A Pyrolysis-Gas-Liquid Chromatographic Study", J. Chromatogr. Sci. 16:623-629 (1978).

Headspace analysis has also been applied to samples of human body fluids including saliva, urine, and blood serum. For references on this topic, please refer to Kostelc, et al, "Salivary Volatiles as Indicators of Periodontitis", J. Periodont. Res., 18:185-192 (1980); Matsumota, et al, "Identification of Volatile Compounds in Human Urine", J. Chromatogr., 85:31-34 (1973); Zlatkis, et al, "Concentration and Analysis of Volatile Urinary Metabolites", J. Chromatogr. Sci., 11:299-302 (1973); Liebich, et al, "Volatile Substances in Blood Serum: Profile Analysis and Quantitative Determination", J. Chromatogr., 142:505-516 (1977).

There remains a need for a non-invasive method for detecting the presence of lung cancer at an early stage, a method which, unlike the conventional invasive procedure, people will not be reluctant to undergo and which will thereby enhance early detection.

SUMMARY OF THE INVENTION

The present invention provides a novel method for screening an individual to determine whether there is an increased probability that he has brochogenic carcinoma. The method comprises the steps of (a) collecting a sample of expired lung air from that individual; and (b) presenting that sample to an indicator means which responds to at least one diagnostically indicative compound in that sample, whereby a positive response to said indicative compound diagnoses the existence of bronchogenic carcinoma.

Using sensitive analytical techniques, it has been found that people suffering from bronchogenic carcinoma (commonly, lung cancer) are more likely to produce certain distinctive compounds in their lungs which are present and detectable in expired air, and to produce those compounds in higher concentrations. People who do not suffer from this disease produce significantly lower or none of these compounds. In accordance with the present invention, an

appropriate indicator means for sensing the presence of these compounds is used to test expired lung air. In a preferred embodiment of the invention, the compounds tested for are aniline and ortho-toluidine (2-methylaniline). The present method provides a non-invasive procedure for diagnosing lung cancers, particularly at an early stage when the prognosis is better, and as such can be used for screening, to detect lung cancers even before symptoms are discernible and therefore before the more invasive detection means conventionally used would be employed.

A preferred indicator for use in the present invention is a gas chromatograph (GC) and/or a GC combined with a mass spectrometer (GC/MS). To aid in the evaluation of the lung air sample, the GC may preferrably be fitted with a nitrogen specific detector which will aid in identifying nitrogen-containing compounds, thereby more easily enabling one who analyzes the chromatograph-generated data to identify the presence of aniline or ortho-toluidine in the test substances.

Since the above-identified compounds are specifically related to the disease process, monitoring the presence and abundance of these compounds in lung air over a period of time serves further diagnostic functions: whether changes in the disease state have occurred, and if so, how the extent of those changes; and whether treatment has halted or reversed the disease process. As a result, a significant diagnostic tool is provided by the present invention which should enhance early detection and treatment of bronchogenic carcinoma.

DETDESC:

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a result of applicants' experimental confirmation that organic constituents of expired lung air are representative of organic compounds being produced in lung tissue and of volatiles in the blood which are in equilibrium with lung fluid and tissue. Volatile organic constituents of lung air are thought to be in equilibrium with a number of systems within the lung, and the presence of many of these constituents is attributed to endogenous or absorbed volatile substances circulating in the blood stream. In addition, certain substances in lung air may be in equilibrium with aveolar fluid or lining material. Finally, mucous glands and cells within the air spaces, tumor cells or cells which are attached to the bronchial epithelium, such as aveolar macrophages, may also contribute to the constituents of lung air.

The experimental confirmation of this invention was performed using gas chromatography (GC) and gas chromatography-mass spectrometry (GC/MS). These techniques have allowed the evaluation of a large number of volatile constituents whose relationship to the bronchial health of human subjects had previously been unexamined. The confirming tests have been conducted as described below.

A total of 16 control subjects were used in the study. Eight (age range 22-41) were recruited from the Interstitial Lung Disease Program at the Hospital of the University of Pennsylvania. Eight aged-matched control subjects (age range 57-66) were recruited from amongst employees of the Monell Center and the Skin Study Center of the University's Dermatology Department. These volunteers met the following criteria: (1) no symptoms of chronic or acute pulmonary

disease; (2) no history of exposure to industrial dust or particulates; (3) normal chest x-ray; and (4) no medication at the time of the study. Among the control subjects, "non-smokers" were defined for purposes of this study as those who had abstained completely from tobacco products for at least five years. Those classified by this study as "smoking" control subjects were smoking between one-half and two packs of cigarettes per day, but did not exhibit symptoms of chronic bronchitis as defined by the American Thoracic Society.

Ten patients, suspected of having bronchogenic carcinoma, were drawn from the Pulmonary Clinic at the Hospital of the University of Pennsylvania. The patients were evaluated with respect to smoking history and with respect to exposure to suspected carcinogens in their industrial or occupational environments. This patient population included seven males, (aged 66, 68, 68, 77, 76, 63 and 70) and three females (aged 59, 62 and 54). All were or had been heavy smokers, although five of the male patients had stopped smoking over three years before the study. Each patient donated a sample of lung air on that patient's initial visit to the clinic, prior to diagnosis and treatment. Subsequent x-ray, bronchoscopy, and biopsy confirmed the diagnosis of either squamous cell carcinoma (6 patients), undifferentiated large cell carcinoma (2 patients) or adenocarcinoma (2 patients).

All participants in this study were asked to exhale end-expiratory air into a tube connected to a 20 liter Tedlar bag (Cole-Palmer Inc.). The bags were immediately returned to a laboratory and the contents transferred, by means of a vacuum pump, to a frosted glass collection tube containing 300 mg of Tenax, 60/80 mesh. Tenax is a porous organic polymer which absorbs organic constituents with little or no retention of water. It is available from the Applied Science Laboratory, State College, Pa. The collection tubes were sealed and frozen until analyzed.

GC and GC/MS were used to analyze the mixtures of these test substances. The organic materials collected on the Tenax traps were desorbed from the polymer by rapidly heating the collection tube to 240o C., and sweeping the volatiles in a helium stream over a 3 minute period into the first 15-20 cm of a nitrogen cooled chromatograph capillary column. Following this, the cooling apparatus was removed from the column, the collection tube was removed from the injection port, a carrier gas flow was resumed through the column, and the chromatograph's oven was brought to its starting temperature of 60o C.

A Finnegan 4510 GC/MS equipped with a split/splitless injector, a fused silica capillary column, and capability for operation in both electron impact and chemical ionization modes were used for the analysis. Components were separated on a CP Wax-57 CB column (25 meters x 0.32 mm) with a 1.2 micron coating. The GC was programmed from 60o C. (with a 4 minute hold period) to 220o C. at 3o /minute. The spectrometer was connected to a Nova 3 computer, which utilizes software for data acquisition and analysis, including a library of 31,000 known compounds. The mass range of m/z 40-450 was scanned once each second and a typical run included 4000 1-second scans. Identifications were based on comparison of the unknown spectra with the 31,000 compound library and manual interpretation of the resulting comparison with mass spectra generated from commercially available standard compounds. In addition, the relative chromatographic retention times of unknown and known standards were compared. A series of C2-C18 fatty acid ethyl esters were used as relative retention time standards. In the case of the anilines, authentic samples were used for

comparison of retention times (scan numbers), mass spectra and obtaining standard curves for quantitation.

Table 1 lists all the major compounds found in the combined study of the patient and control populations. The compounds in the table are divided into those thought to be of metabolic origin, those thought to be from exogenous sources (including food and environmental exposure), and those (three compounds) whose origins were not capable of probable categorization. The major components in the lung air from patients with lung carcinoma and control subjects (regardless of age) are qualitatively similar. However, differences in several minor components were discernible after careful examination of each peak in the reconstructed ion chromatograms generated by the collected lung air constituents.

TABLE 1

Metabolic origin	Exogenous origin
isoprene	toluene
acetone	limonene
dimethyldisulfide	styrene
pyridine	octylacetate
acetoin	menthol
benzaldehyde	terpineol
hexanol	butylated hydroxytoluene
pentanone	benzothiazole
acetophenone	diphenylamine
cumene alcohol	iso-octanol
dodecanol	
phenol	Other
cresol	
indole	benzonitrile
	aniline
	o-toluidine

Aniline and o-toluidine were initially found in the expired lung air of one carcinoma patient. Subsequently, the corresponding retention time window of chromatograms generated from all participants were searched for these compounds according to the key ions in their mass spectrum (m/z 93,66 for aniline; m/z 06,107 for o-toluidine). Aniline was found in 5 of the 10 cancer patients, none of the aged-matched controls (55-66 yrs), and 2 of the 8 younger (22-41 yrs) controls. Ortho-toluidine was found in of the 10 cancer patients, 3 of the 8 younger controls and 6 of 8 aged-matched controls. The level of o-toluidine found in the cancer patients was significantly higher than the level found in either control group and all but one of the 4 controls whose air samples did contain it. Table 2 summarizes the results of the analysis for the presence of aniline and o-toluidine in the control/patient population. The data in Table 2 were analyzed to determine if the levels of aniline and o-toluidine seen in controls was different than patients.

The data presented in Table 2 show that levels of aniline and o-toluidine will most likely be elevated in people with bronchogenic carcinoma.

Ortho-toluidine was found in significantly elevated levels in patients with lung air when compared to either aged-matched ($T = 2.217$; $df = 16$; $p < 0.05$) or younger controls ($T = 2.14$; $df = 16$; $p < 0.05$). The highest levels of aniline were found in 4 of the 6 patients with squamous cell carcinoma suggesting a possible relationship between this cell type and production of the aniline. Consequently, levels of o-toluidine equal to or greater than the mean level of carcinoma patients in conjunction with measurable levels of aniline would suggest the increased probability of carcinoma.

TABLE 2
Presence of Aniline and O-Toluidine in Patient/Control Population

Population					Concentration ng/20 L Lung Air	
Patient	Age	Sex	Smoking<1>	Diagnosis<2>	Aniline	O-Toluidine
1	66	M	SS8; > 30 pk yrs.	Squamous Cell	2.01	6.26
2	59	F	S; > 40 pk yrs.	Squamous Cell	17.56	9.55
3	68	M	SS3; > 40 pk yrs.	Squamous Cell	13.87	19.45
4	68	M	SS5; > 40 pk yrs.	Squamous Cell	ND	5.26
5	77	M	SS10; > 50 pk yrs.	Squamous Cell	24.08	9.00
6	70	M	S; > 40 pk yrs.	Squamous Cell	ND	ND
7	62	F	SS1; > 40 pk yrs.	Undiff. large cell	ND	1.53
8	76	M	SS15; > 30 pk yrs.	Undiff. large cell	ND	2.24
9	54	F	S; > 40 pk yrs.	Adenocarcinomia	7.44	6.20
10	63	M	S; > 45 pk yrs.	Adenocarcinomia	ND	8.77
Age - Matched Controls (57-66)						
AC1	66	M	S; > 45 pk yrs.		ND	0.181
AC2	64	M	S; > 40 pk yrs.		ND	2.94
AC3	57	F	S; > 25 pk yrs.		ND	4.30
AC4	55	M	S; > 30 pk yrs.		ND	2.82
AC5	54	F	NS		ND	4.92
AC6	58	F	SS1; > 40 pk yrs.		ND	2.94
AC7	63	F	NS		ND	ND
AC8	59	M	NS		ND	ND
Young - Controls (22-41)						
YC1	27	F	S; > 5 pk yrs		ND	ND
YC2	24	M	NS		ND	ND
YC3	25	F	S; > 8 pk yrs.		ND	ND
YC4	27	F	NS		ND	2.80
YC5	22	F	NS		8.6	ND
YC6	41	F	SS6; > 15 pk yrs.		ND	ND
YC7	34	F	S; > 16 pk yrs.		5.89	11.05
YC8	22	F	NS		ND	0.88

n<1> "S" = smoker; "NS" = non-smoker; "SSX" = stopped smoking x yrs prior to study; pk yrs = pack years -

n<2> Diagnosis by cell type which were either Squamous Cell Carcinoma; Undifferentiated Large Cell Carcinomia or Adenocarcinoma -

n<3> Quantitation is based on the amount recovered from 20 L bags. The efficiency of transfer of aniline and o-toluidine from the bags to gas chromatograph/mass spectometer system is approx. 10%; ND = not detected, below instrument detection threshold which is approximately 0.1 picograms. -

The majority of compounds listed in Table 1 have already been reported by others, or are similar to those that have been reported by others, as being volatile constituents of either respiratory air or other body specimens. See, for example, A. Zlatkis, R. Brazell, and C. Poole, Clin. Chem., 27:289-297 (1981). B. Krotoszyinski, G. Gabriel and H. J. O'Neill, Chrom. Sci., 15:239 (1977). Many volatile nitrogen-containing compounds, such as heterocyclics (pyrroles, indole, pyridines, pyrollines), aliphatic amines, and benzylamine, which is a structural isomer of o-toluidine, are among the reported compounds identical to or similar to those of Table 1. Alkyl pyridines have been detected in headspace over human saliva and are believed to be a breakdown product of collagen. See J. Kostelc, P. Zelson, G. Preti and J. Tonzetich, Clin. Chem., 27:842-845 (1981). Menthol, although detected in the air samples obtained from several of the cancer patients, is a pervasive compound, being present in cigarettes as well as personal health and toiletry preparations, and consequently was thought to be exogenous rather than tumor-related.

Aniline, methylanilines, and N-ethyl and N, N-dimethyl-anilines have been reported in cigarette smoke. Specifically, levels of aniline and o-toluidine have been reported as 364 ng and 162 ng, respectively, in main stream cigarette smoke and considerably higher in sidestream cigarette smoke. See C. Patrianakos and D. J. Hoffmann, Anal. Toxic, 3:150-154 (1979). H. Sakuma, K. Kusama, K. Yamaguchi, T. Matsuki, and S. Sugawara, Beitrage Tabakforschung Int., 12:199-209 (1984). Nevertheless, aniline detected in this study in the lung air samples of the cancer patients, all of whom smoke, was not attributed to cigarettes since aniline was detected in only one of the five smoking control participants. Similarly, o-toluidine was detected in all four smoking cancer patients but in only three of the five smoking control participants; in two of those controls, the detected level of the compound was significantly lower than that in any of the cancer patients.

Aniline has been reported with diphenylamine and benzothiazole, to be present in various industrial emissions. See D. Lane, B. Thampson, A. Lovett and N. Reid, Adv. Mass Spectrom., 8B:1480-1489 (1980). However, diphenylamine and benzothiazole were found in all participants of this study, whereas aniline was not found in all but rather was present at a statistically significantly higher level in five of the cancer patients, particularly those with squamous cell carcinoma.

From the accumulation and analysis of this data, applicants have concluded that aniline and o-toluidine originate from a physiological process, not presently known, that is linked to bronchogenic tumor formation or growth. These anilines are not believed to be exogenous in origin, nor has the present study linked their presence to bacterial colonization of tumors, a phenomenom that has

previously been reported. See I. McGregor, J. Watson, G. Sweeney and J. Sleigh, Lancet, I:110 (1982). Accordingly, the presence of aniline or o-toluidine in expired lung air at the concentration seen in the cancer patients described here is suggestive of bronchogenic carcinoma.

The preferred indicator means of this invention allows the screening of expired lung air to detect the presence of these two diagnostically indicative compounds at levels of parts per million or parts per billion. It is within the scope of the present invention, however, to use alternate indicator means which can be more or less sensitive than those described herein. For example, the organic constituents of the expired lung air sample can be detected and quantified using a variety of different methodologies, including colorometric and/or immunoreactive tests.

CLAIMS: We claim:

[*1] 1. A method for screening an individual to determine the probability of bronchogenic carcinoma in that individual comprising the steps of:

(a) collecting a sample of expired lung air from that individual; and

(b) presenting that sample to an indicator means which responds specifically to a diagnostically indicative compound in that sample, said indicative compound being selected from the group consisting of aniline and o-toluidine, whereby a positive response to said indicative compound indicates an increased probability of biochogenic carcinoma.

[*2] 2. The method of claim 1 wherein step (b) comprises providing an indicator means responsive to aniline.

[*3] 3. The method of claim 2 wherein said indicator means also respond quantitatively.

[*4] 4. The method of claim 3 which further comprises the steps of (c) repeating steps (a) and (b); and (d) comparing the response from the later performed step (b) with the earlier performed step (b) to monitor a change in the disease state.

[*5] 5. The method of claim 1 wherein step (b) comprises providing an indicator means responsive to o-toluidine.

[*6] 6. The method of claim 5 wherein said indicator means also respond quantitatively.

[*7] 7. The method of claim 1 wherein said indicator means also respond quantitatively to said indicative compound.

[*8] 8. The method of claim 7 wherein said quantitative response is compared to normal control amounts, whereby a higher concentration of said compound is indicative of a higher probability of said carcinoma.

[*9] 9. The method of claim 8 which further comprises the steps of (c) repeating steps (a) and (b); and (d) comparing the response from the later performed step (b) with the earlier performed step (b) to monitor a change in

the disease state.

[*10] 10. The method of claim 7 which further comprises the steps of (c) repeating steps (a) and (b); and (d) comparing the response from the later performed step (b) with the earlier performed step (b) to monitor a change in the disease state.

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Apr. 5, 1988

Instrument for parallel analysis of metabolites in human urine and expired air

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REF-CITED:

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ABST:
An apparatus for measuring metabolites contained in human expired air and for measuring metabolites contained in human urine and for extracting a correlation between the metabolite data in the expired air and the metabolite data in the urine is suitable for parallel analysis of the metabolites in human urine and expired air. An atmospheric pressure ionization mass spectrometer is suitable for measuring metabolites in the expired air. By storing reference data showing the relation between the metabolites in the expired air and those in the urine and, by comparing such data with a subject's metabolite data in the expired air and the metabolite data in the urine, abnormality of a subject can be detected.

NO-OF-CLAIMS: 15

EXMPL-CLAIM: <=3> 1

NO-OF-FIGURES: 6

NO-DRWNG-PP: 6

SUM:

BACKGROUND OF THE INVENTION

This invention relates to an apparatus for measuring metabolites in living bodies. More particularly, this invention concerns an apparatus for parallel analysis of metabolites in human urine and expired air by a non-invasive method suitable for obtaining information effective for diagnosis and elucidation of metabolism by simultaneously mesuring metabolites in the expired air and urine.

As a means for executing a health examination and elucidating metabolism in human bodies, there is measurment of metabolites. As a sample, blood is generally used, but there are defects in that the sampling of blood puts a burden on subjects and further continuous measurement on the same subject is impossible. In contrast, non-invasive measurement of metabolites using as a sample urine or expired air naturally excreted from a human body or the gas diffused from the skin can reduce the burden on the subjects. But since the metabolism of the human body is very complicated, it is important to effect judgement based on not a single information but rather on a plurality of information in order to give a clearer diagnosis.

Heretofore, as to the urine, various components such as proteins,

saccharides, vitamins, etc. in the urine are measured and used for practical clinical laboratory tests.

As to metabolites in the expired air, since the amounts thereof are very trace (usually the level of ppb or less) and the measurement is very difficult, there are only a few reports which detect organic substances in the expired air, for example, B. Krotoszynski, G. Gabriel, H. O'Neill, and M. P. A. Claudio: J. Chromatographic Sci. vol. 15, pp. 239-244 (1977).

According to known non-invasive metabolite measuring methods, urine and expired air are measured independently. Particularly, since the detection of metabolites in the expired air is difficult, there has been no report as to the simultaneous measurement of metabolites in the urine and metabolites in the expired air. Therefore, no study has been made on the relationship between the metabolism as to the urine and that as to the expired air, which relationship can be a basis for clearer diagnosis and more suitable thereby based on a plurality of information and non-invasive sampling.

SUMMARY OF THE INVENTION

It is an object of this invention to provide an apparatus for parallel analysis of metabolites in human urine and expired air for measuring metabolites in the expired air and metabolites in the urine at the same time and for obtaining information on the metabolites from different metabolic routes.

It is another object of this invention to provide an apparatus for parallel analysis of metabolites in human urine and expired air in order to make it possible to detect an abnormality of a subject based on the correlation between the metabolites in the expired air and the metabolites in the urine.

This invention provides an apparatus for parallel analysis of metabolites in human urine and expired air comprising

a means for measuring expired air to determine metabolites contained in the expired air,

a means for measuring urine to determine metabolites in the urine simultaneously sampled with the expired air, and

a means for extracting the correlation between the metabolites in the expired air and the metabolites in the urine from metabolite data determined by the expired air measuring means and metabolite data determined by the urine measuring means.

This invention also provides an apparatus for parallel analysis of metabolites in human urine and expired air comprising

a means for measuring expired air to determine metabolites contained in the expired air from a subject,

a means for measuring urine to determine metabolites in the urine from the subject simultaneously sampled with the expired air,

a means for storing data showin the relation between the metabolites in the expired air and the metabolites in the urine, and

a means for detecting an abnormality of the subject by comparing the relation between metabolite data in the expired air determined by the expired air measuring means and metabolite data in the urine determined by the urine measuring means with the data showing the relation between the metabolites in the expired air and the metabolites in the urine stored in the storing means.

As the expired air measuring means, it is effective to use an atmospheric pressure ionization mass spectrometer comprising an ion source for ionizing an expired air sample under an atmospheric pressure, a high vacuum portion wherein a mass analyzer and an ion collector are installed, and an intermediate pressure portion placed between the ion source and the high vacuum portion.

DRWDESC:
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic diagram showing one example of the apparatus for parallel analysis of metabolites in human urine and expired air according to this invention.

FIG. 2 is a flow chart showing one example of operations of the computer system 4 in FIG. 1.

FIG. 3 is a graph showin a relationship between the concentration of acetone in expired air of healthy persons and subjects suffering from diabetes mellitus.

FIGS. 4 and 5 are graphs showing a relationship between acetone in expired air and adrenaline or noradrenaline which is a metabolite in the urine.

FIG. 6 is a flow chart showing another example of operations of the computer system 4 in FIG. 1.

DETDESC:

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention is illustrated referring to the drawings.

FIG. 1 shows one example of the apparatus for parallel analysis of metabolites in human expired air and urine according to this invention, wherein an atmospheric pressure ionization mass spectrometer 1 and a liquid chromatograph 2 are connected to a computer system 4 via an interface 3. Trace amounts of metabolites in the expired air are measured by the atmospheric pressure ionization mass spectrometer 1 and amounts of metabolites in the urine are measured by the liquid chromatograph 2.

The atmospheric pressure ionization mass spectrometer 1 contains a mouthpiece or a sampling vessel 5 for sampling expired air. When the expired air is sampled on-line, the mouthpiece is used, while when sampled off-line, a bag containing the expired air is attached to the sampling vessel 5. The expired air sampled by the sampling vesel 5 is introduced to an ion source 8 directly or via an expired air sample concentrating device 6. The expired air sample concentrating device 6 is constructed, for example, to contain an absorbent for absorbing the metabolites in the expired air inside thereof, the absorbent being heated so as

to release the metabolites when a high metabolite concentration is attained. Those ionized by the ion source 8 are introduced into an analyzing portion 10 which is a high vacuum portion via an intermediate pressure portion 9 and the ions are mass separated by a quadrapole mass analyzer 11 and detected at an ion collector 14, wherein the metabolites in the expired air is determined. The ion current proportional to the quantity of metabolites and obtained in the collector 14 is transmitted to the interface 3 via an amplifier 15. The intermediate pressure portion 9 and the high vacuum portion 10 are maintained at the predetermined pressure by vacuum pumps 13, 12, respectively.

In the liquid chromatograph 2 for detecting the metabolites in the urine, a urine sample from a urine sampling vessel 16 is introduced to a liquid chromatograph separation column 18 directly or via a urine sample concentrating device 17. The sample passed the column 18 is transmitted to a liquid chromatograph detector 19 to determine the metabolites in the urine. The output of the detector 19 is transmitted to the interface 3.

Using the above-mentioned apparatus, the expired air sample and the urine sample obtained from the same subject at the same time can be analyzed at the same time, that is, the expired air is analyzed by the atmospheric pressure ionization mass spectrometer 1 and the urine is analyzed by the liquid chromatograph 2. The atmospheric pressure ionization mass spectrometer 1 is very sensitive (ppt level) to gaseous samples, and thus enables detection of trace amount of volatile metabolites contained in the expired air. The liquid chromatograph 2 enables detection of non-volatile high molecular weight metabolites contained in the urine. In order to pass the expired air sample to the ion source 8, an expired air sampling device or an expired air sample introducing device 5 is combined to the atmospheric pressure ionization mass spectrometer 1. In the case of on-line sampling wherein the expired air sample from a subject is directly passed to the ion source 8, the mouthpiece and the ion source 8 are combined by a sample introducing pipe. On the other hand, in the case of off-line sampling wherein a subject and the apparatus are positioned with a long distance, an expired air sampling vessel (e.g. a bag made of a plastic film) can be attached to the apparatus. In the case of a urine sample, a urine sampling device or a urine sample introducing device 16 is combined to the liquid chromatograph 2 similarly. The sampling device or the introducing device for the expired air sample or urine sample can be equipped with a heating means 7 for providing variable temperatures in order to prevent the inner surface of the introducing pipe or the sampling vessel from the adsorption of the sample which is in a trace amount. In the case of measuring ultra-trace amounts of metabolites which cannot be measured by the atmospheric pressure ionization mass spectrometer and the liquid chromatograph, a sample concentrating means 6 and 17 can be provided in a proper portion of the introducing pipe.

The atmospheric pressure ionization mass spectrometer 1 and the liquid chromatograph 2 thus constituted are controlled by the computer system 4, respectively. The role of the computer system 4 is illustrated referring to FIG. 2 showing a flow chart.

First, an expired air sample and a urine sample of a subject (i) are measured by the atmospheric pressure ionization mass spectrometer 1 and the liquid chromatograph 2 under the control of the computer system 4 in the step 20. In the step 21, the measured data are acquired to the computer system 4 on-line via the interface 3. In the step 22, the amounts of metabolites (j) in

the expired air (Bij) are determined from the expired air data of the subject (i) collected. In a similar manner, the amounts of metabolites (k) in the urine (Uik) are determined. In the step 23, correlation between the metabolites (j) in the expired air and the metabolites (k) in the urine is checked (calculation of a correlation coefficient gamma jk) by the computer system 4 in order to fine information which cannot obtained by the expired air sample data alone and the urine sample data alone.

The correlation coefficient gamma jk is calculated by the following equation:
[See Original Patent for Chemical Structure Diagram]

In practice, there are detected several hundred peaks in the expired air spectrum obtained by the atmospheric pressure ionization mass spectrometer 1 (the value of j has several hundred ones). There are also detected several hundred peaks in the urine spectrum obtained by the liquid chromatograph 2 (the value of k has several hundred ones). Therefore, in order to check the correlation between these numerous peaks, it is very difficult to compute without using a computer. Further, when the number of subjects (i) increases, the calculation becomes almost impossible.

In the step 24, the degree of correlation between the metabolites in the expired air (j) and the metabolites in the urine (k) obtained by the computer system 4 is displayed, and if required, a scatter diagram R(jk) obtained by extracting data particularly having strong correlation can be displayed on a display device 25.

According to this invention, the following effects can be obtained. When the human expired air is analyzed by the atmospheric pressure ionization mass spectrometer 1 which is one constituent of the apparatus of this invention, acetone which is a trace amount metabolite (in a concentration of 10 ppb to several hundreds ppb in the human expired air) can be detected. FIG. 3 shows acetone concentrations in expired air of normal healthy persons (persons showing no abnormality in a usual medical examination) and subjects suffering from diabetes mellitus. The acetone concentration in the expired air of the subjects suffering from diabetes mellitus is higher than that of the normal healthy persons. This is because in the case of the diabetes mellitus, the decomposition of lipids is activated by the lack of sugars in the body, and as a result, the concentration of ketone body in the blood increases, which results in including acetone in expired air in lungs, the acetone being a volatile substance in the ketone body. As mentioned above, it is possible to diagnose diabetes mellitus non-invasively by the atmospheric pressure ionization mass spectrometer 1 without sampling blood and without putting a burden on a subject.

But sometimes the acetone concentration in the expired air of normal healthy persons is as high as that of subjects mildly suffering from diabetes mellitus as shown in FIG. 3. Such a case can be admitted on about 10% of total normal healthy persons examined. Such a value is very large from the medical point of view. In order to achieve a more correct, such a case should be distinguished from the diabetes mellitus.

In order to attain such an object, metabolites in the urine of such subjects are measured by the liquid chromatograph 2 and at the same time the acetone in

the expired air is measured by the atmospheric pressure ionization mass spectrometer 1, and the correlation between the acetone in the expired air and the metabolites in the urine is examined by the computer system 4 with the following results. That is, even in the case of normal healthy persons, when the
acetone concentration in the expired air is high, the amount of catechol amines (adrenaline and noradrenaline) in the urine increases (see FIGS. 4 and 5). On the other hand, when the same measurement is carried out as to the subjects suffering from diabetes mellitus, there is no correlation between the acetone in the expired air and the catechol amines in the urine. These results show that it is possible to distinguish the example of high acetone concentration in the expired air of normal healthy persons from the example of diabetes mellitus non-invasively, which provides an improved diagnosis.

An important finding in these results is a new finding that a cause for increasing the amount of acetone in the expired air of even normal healthy persons (excluding the influence of meals, fatigue, etc.) relates to the catechol amines. No report has been made as to the relation between the catechol amines in the urine and the acetone in the expired air and the present inventors have found this fact for the first time.

Catechol amines are secreted from the adrenal body under a tension state and are substances which can cause arterial sclerosis of a heart. Usually, the catechol amines are transient. But the examples wheren the amount of acetone in the expired air is large even in the case of normal healthy persons as shown in FIGS. 3, 4 and 5 are examples wherein the amount of acetone in the expired air is always large even when measured for a long period of time of one year. Thus the fact that catechol amines are continuously secreted in large amounts for such a long period of time seems to be one cause for heart disease. Therefore, by carrying out the above-mentioned measurement on normal healthy persons periodically, such a measurement can be one means of preventive medicine for the heart disease. Usually, normal healthy persons have a strong tendency to dislike the taking of blood samples, but, the above-mentioned measurement reduces the burden of subjects compared with conventional blood sampling and, thus, makes such subjects more agreeable to the test.

As mentioned above, by using the apparatus of this invention, the strong correlation between the acetone in the expired air and the adrenaline and noradrenaline in the urea can be grasped. Further, it is also possible to grasp relations among various substances by measuring a number of subjects in various states. This invention is effective not only in providing novel information in the medical field but also in applying the apparatus in practical diagnosis as mentioned below.

The apparatus used for practical diagnosis is explained referring to FIG. 1 and the flow chart of FIG. 6. As shown in the step 27 in FIG. 6, new information data as shown in FIGS. 4 and 5 are stored in a data file 26 shown in FIG. 1 as reference data R(jk). In the step 28, an expired air sample and a urine sample of a subject (patient) a are measured, expired air data and urine data are collected in the step 29, and the amounts of metabolites j in the expired air (Baj) and the amount of metabolites k in the urine (Uak) are determined in the step 30. In order to know whether the data of the patient a (Baj, Uak) are normal or abnormal, comparison is made between the reference data R(jk) stored in the data file 26 and the measured data (Baj, Uak). This can be done, for

example, as shown in the step 31, wherein the reference data R(jk) are displayed on the display device 25 as a scatter diagram and the measured data (Baj, Uak) are plotted on the displayed reference data. By doing this, differences between the reference data and the patient data can be readily seen. Then, medical doctors can decide upon a diagnosis and treatment for the patient.

In the above explanations, the atmospheric pressure ionization mass spectrometer is used as a device for measuring the metabolites in the expired air, but is is possible to use a gas chromatograph for measuring volatile metabolites in the expired air. The sensitivity of the gas chromatograph is not as good, but the cost can be reduced remarkably. In addition, it is possible to use a gas chromatograph or the same atmospheric pressure ionization mass spectrometer as used for measuring the metabolites in the expired air as a device for measuring the metabolites in the urine in order to measure volatile substances in the urine.

As constituent elements of the apparatus of this invention, it is possible to use a gas chromatograph-mass spectrometer (GC-MS) for measuring metabolites in the expired air and urine other than mentioned above. Further, it is possible to use an electrophoretic device for measuring the metabolites in the urine.

As mentioned above, according to this invention, the metabolites in the urine and the metabolites in the expired air can be measured at the same time, and the relationships among individual metabolites can be studied for comparison, so that new phenomena heretofore not known as to the metabolism can be determined. Further, the apparatus of this invention does not put a burden on a subject. Therefore, short interval tests as to the diagnosis and remedy for various diseases such as diabetes mellitus, heart disease, etc. become possible compared with the conventional blood tests.

CLAIMS: What is claimed is:

[*1] 1. An apparatus for parallel analysis of metabolites in human urine and expired air comprising

means for measuring expired air to determine metabolites in the expired air of a person to be examined,

means for measuring urine to determine metabolites in the urine of the person to be examined which is substantially simultaneously sampled with the sampling of the expired air of the person;

means for storing data of metabolites in the expired air measured by the expired air measuring means and data of metabolites in the urine measured by the urine measuring means, and

correlation extracting means for generating a correlation between the metabolites in the expired air and the metabolites in the urine from the metabolites data.

[*2] 2. An apparatus according to claim 1, wherein the urine measuring means is a liquid chromatograph.

[*3] 3. An apparatus according to claim 1, wherein the expired air

measuring means has a sample concentrating means for concentrating the expired air sample gas.

[*4] 4. An apparatus according to claim 1, wherein the expired air measuring means includes means for measuring volatile metabolites contained in the expired air and provides output data indicative thereof, and the urine measuring means includes means for measuring non-volatile metabolites contained in the urine and provides an output indicative thereof, the correlation extracting means generating a correlation between the volatile metabolites in the expired air and the non-volatile metabolites in the urine.

[*5] 5. An apparatus according to claim 1, wherein the expired air measuring means includes means for measuring acetone in the expired air and provides output data indicative thereof, and the urine measuring means includes means for measuring catechol amine in the urine and provides output data indicative thereof, the correlation extracting means generating a correlation between the measured acetone in the expired air and the measured catechol amine in the urine of the person.

[*6] 6. An apparatus according to claim 1, wherein the correlation extracting means includes means for calculating a correlation coefficient for the measured metabolites of the expired air and the urine of the person.

[*7] 7. An apparatus according to claim 1, wherein the expired air measuring means is an atmospheric pressure ionization mass spectrometer comprising an ion source for ionizing an expired air sample udner an atmospheric pressure and a high vacuum portion having a mass analyzer and an ion collector disposed therein.

[*8] 8. An apparatus according to claim 7, wherein the atmospheric pressure ionization mass spectrometer further comprises an intermediate pressure portion disposed between the ion source and the high vacuum portion.

[*9] 9. An apparatus for parallel analysis of metabolites in human urine and expired air comprising:

means for measuring expired air to determine metabolites contained in the expired air from a subject,

means for measuring urine to determine metabolites in the urine from the subject simultaneously sampled with the expired air,

means for storing metabolites data determined from the measured expired air and the measured urine of the subject and for storing reference data showing a relation between the metabolites in the expired air and the metabolites in the urine, and

comparison means for comparing a relation between the subject metabolites data in the expired air determined by the expired air measuring means and the subject metabolites data in the urine determined by the urine measuring means with the stored reference data showing the relation between the metabolites in the expired air and the metabolites in the urine so as to detect an abnormality of the subject.

[*10] 10. An apparatus according to claim 9, wherein the expired air measuring means is an atmospheric pressure ionization mass spectrometer comprising an ion source for ionizing an expired air sample under an atmosphere pressure, a high vacuum portion having a mass analyzer and an ion collector disposed therein and an intermediate pressure portion disposed between the ion source and the high vacuum portion.

[*11] 11. An apparatus according to claim 9, wherein the expired air measuring means includes means for measuring volatile metabolites in the expired air and provides output data indicative thereof, and the urine measuring means includes means for measuring non-volatile metabolites in the urine and provides output data indicative thereof, the storing means includes means for storing reference data showing a relation between the volatile metabolites in the expired air and the non-volatile metabolites in the urine, and the comparison means includes means for displaying the stored reference data showing the relation between the volatile metabolites in the expired air and the non-volatile metabolites in the urine stored in the storing means in the form of a scatter diagram and for displaying the stored subject metabolites data in the expired air and in the urine of the subject on the same displayed scatter diagram.

[*12] 12. An apparatus according to claim 9, wherein the expired air measuring means includes means for measuring acetone in the expired air and provides output data indicative thereof, and the urine measuring means includes means for measuring catechol amine in the urine and provides output data indicative thereof, storing means storing reference data showing a relation between acetone in the expired air and the catechol amine in the urine, and said comparison means detects an abnormality by enabling comparison of a relation between the stoned subject metabolite output data of acetone in the expired air from said expired air measuring means and output data of the catechol amine in the urine from the urine measuring means with the stored reference data showing the relation between the acetone in the expired air and the catechol amine in the urine.

[*13] 13. An apparatus according to claim 9, wherein the comparison means includes display means for displaying the stored reference data showing the relation between the metabolites in the expired air and the metabolites in the urine stored in the storing means in the form of a scatter diagram and for displaying the stored subject metabolite data in the expired air and in the urine on the same displayed scatter diagram.

[*14] 14. An apparatus according to claim 9, wherein the comparison means includes means for calculating a correlation coefficient for the metabolite data from the expired air measuring means and the urine measuring means.

[*15] 15. An apparatus for parallel analysis of metabolites in human urine and expired air comprising:

expired air measuring means for measuring acetone in an expired air from a subject;

urine measuring means for measuring catechol amine contained in the urine of the subject which is sampled at the time of sampling the expired air of the subject;

storing means for storing data of measured acetone and measured catechol amine of the subject and for storing reference data showing a relation between the acetone contained in the expired air and the catechol amine contained in the urine as to diabetes; and

comparison means for comparing stored subject data of the acetone in the expired air detected by the expired air measuring means and the catechol amine in the urine detected by the urine measuring means with the stored reference data showing a relation between the acetone in the expired air and the catechol amine in the urine so as to detect an abnormality of the subject.

175TH PATENT of Focus printed in FULL format.

4,202,352

<=2> GET 1st DRAWING SHEET OF 1

May 13, 1980

Apparatus for measurement of expired gas concentration in infants

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ASSIGNEE-AT-ISSUE: Research Development Corporation, San Francisco, California (02)

ASSIGNEE-AFTER-ISSUE: Date Transaction Recorded: Oct. 24, 1980
ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
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Reel & Frame Number: 3808/0529

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SEARCH-FLD: 128#2.07, 2.08, 2C, 719, 727, 728, 730; 73#123R, 421.5R

REF-CITED:

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3,659,590	5/1972	Jones et al.	128#2.08
3,850,036	11/1974	Sanctuary et al.	73#421.5R
3,896,792	7/1975	Vail et al.	128#2.07
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PRIM-EXMR: Howell, Kyle L.

LEGAL-REP: Flehr, Hohbach, Test, Albritton & Herbert

ABST:
Apparatus for measuring expired gas concentration in infants whose breathing rate is too high for normal analyzers by sampling the breath, for instance from the tube between the respirator and the infant, and drawing that sample of gas into an elongated, small diameter tube which serves to store the sample in a linear array substantially without intermixing. Several breaths are thus stored after which time the sampling may be interrupted and the stored gas drawn slowly

through a gas analyzer.
NO-OF-CLAIMS: 10

EXMPL-CLAIM: <=7> 1

NO-OF-FIGURES: 1

NO-DRWNG-PP: 1

SUM:

BACKGROUND OF THE INVENTION

In the treatment of infants with respiratory disease it can be of great importance to measure the concentration of carbon dioxide and oxygen in the expelled air of the infant. It is even more useful if these gases, particularly the carbon dioxide, can be measured at the end of expiration so as to obtain the highest carbon dioxide concentration of the expiration, usually called end-tidal peak carbon dioxide (ECO2). Likewise, in the study of infants liable to "Sudden Infant Death Syndrome", the measurement of end-tidal peak carbon dioxide can be of critical importance because such infants may hypoventilate with a rising ECO2 before going into apnea and dying.

In adults, who breathe at a rate of about 20 breaths per minute, it is relatively easy to take measurements of ECO2. But most current rapid analyzers are limited in their response time to indicating only about 90% of the actual concentration in two tenths of a second. This means that in infants, who breath at a high rate, often over sixty or eighty, the response of a rapid gas analyzer is too slow to pick the peak of the end-tidal carbon dioxide because the next inspiration intervenes before the instrument has a chance to come to equilibrium for a valid measurement. Reliable measurements of end-tidal carbon dioxide in infants have heretofore only been possible using specially adapted mass-spectrometers which are very expensive and even then the end-tidal peak is often blurred by the rapid respiration rate.

Another problem in such measurement with respect to infants is that in order to measure, it is necessary to draw a continuous sample from the airway, typically at the rate of about 0.5 liters per minute and pass that volume through the gas analyzer. But in an infant who is only breathing one or two liters per minute and who is on the partially closed circuit of a ventilator, the half liter is a dangerously large amount to suck out of the airway.
SUMMARY OF THE INVENTION AND OBJECTS

The invention is incorporated in apparatus including means for sampling the gas from an infant's airway and simultaneously returning gas to that airway in the same volume so that there is no net loss of gas from the airway. Means are further provided to discontinue sampling of gas from the airway and thereafter direct the previously drawn sample to a gas analyzer at a relatively slow rate such that the analyzer may come to equilibrium and give valid measurements of end-tidal peak carbon dioxide.

It is, therefore, a general object of the present invention to provide an improved apparatus for measurement of expired gas concentration in infants.

It is a further object of the present invention to provide such an improved apparatus for measuring expired gas concentration in infants wherein accurate measurements can be taken with existing equipment and without subjecting the infant to the dangers of drawing large volumes of gases from the airway.

DRWDESC:
BRIEF DESCRIPTION OF THE DRAWING

The single FIGURE is a schematic diagram of apparatus for measurement of expired gas concentration in infants in accordance with the invention.

DETDESC:

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Referring to the FIGURE there is shown an infant 11 utilizing an airway 13 coupled to a respirator 15. The airway 13 may employ a face mask 17, as shown, or may include an intratracheal tube or the like. The airway 13 includes a baffle 19 extending longitudinally in the area of taps 21 and 23. The baffle 19 serves to isolate the tap 21 from the tap 23 whereby gases going to or from either will not interfere with the gas from the opposite tap.

The tap 21 is connected to a loop of fine tubing 25 through lines 27 and 28 and valve 29. Valve 29 includes an exhaust port 31 and when rotated counterclockwise from the position as shown will serve to connect loop 25 to the atmosphere through the port 31.

The opposite end of the loop 25 is connected by lines 33, 35 and 37 and valves 39 and 41 to a reversible pump 43. The opposite side of the pump 43 is connected to the tap 23 in the airway 13. As shown this route is defined by the lines 45, 47 and 49 together with the valves 51 and 53.

Alternatively, with the valves 51 and 53 rotated 90oclockwise and counterclockwise respectively, from the position shown, the pump 43 is connected to the outer chamber 55 of a captive bag assembly 57. The captive bag 59 of that assembly communicates with the tap 23 through the lines 61, 63 and 49 and the valves 65 and 53. The valve 65 includes an exhaust port 67 which communicates with the interior of the captive bag 59 when the valve 65 is rotated 90oclockwise from the position shown.

The valve 39 includes a port 69 which communicates with the loop 25 when the valve 39 is rotated 90oclockwise from the position shown. Tap 69 further communicates with a rapid gas analyzer 71 through the line 73. Gas from the loop 25 may be drawn through the rapid gas analyzer by means of a pump 75 connected to the analyzer 71 by the line 77. The discharge of the pump 75 may be vented to atmosphere through the line 79.

In the operation of the apparatus with the valves 51 and 53 set as shown in the drawing, the unit operates without using the captive air bag assembly 57. With the valves 29 and 39 set as shown in the drawing the apparatus is set for the first of two phases of operation. In this first phase, which lasts for several seconds or longer, the pump 43 operates to circulate gas from the airway 13 through the valve 31, the loop 25, the valve 39, the pump 43 itself, the valves 51 and 53 to the tap 23 of the airway 13. Phase one operates for a

sufficiently long period of time to permit the infant to breath several breaths.
The tube loop 25 is chosen to be long enough so that the transit time of a gas particle through it is longer than the time required for several breaths at the normal infant respiratory rate. Conveniently, this tube may be about 10 meters long with an internal diameter of 1 millimeter or less with the pump 43 operating at a rate of approximately one-half liter per minute.

Even though the pump draws a half liter of gas per minute from the airway 13 at the tap 21, the same amount of gas is being simultaneously returned to the airway through the tap 23. Consequently, there is no net loss of gas volume in the airway itself.

During the second phase of operation the valve 29 is rotated 90ocounterclockwise from the position shown and valve 39 rotated 90oclockwise from the position shown. The pump 75 is then operated to draw the gas from the loop 25 slowly through the rapid gas analyzer 71. During this phase of operation measurements of gas concentrations are actually made and no gas is drawn from the airway 13. After sufficient time for the gas measurements to be made the system returns to phase one and the operation is repeated.

The apparatus then does not measure every breath of the infant but it does measure several breaths in sequence. If it were felt necessary to measure every breath, multiple apparatus of the type shown could be employed and phased in such a manner that when one is in the first phase of operation the other is in the second phase.

It may be considered advantageous to prevent mixing of the gases at inlet and outlet lines of the loop 25 and if this mode of operation is required the captive gas bag assembly 57 may be employed by rotating the valves 51 and 53 clockwise and counterclockwise respectively for 90o. The line 47 is then incapacitated and during phase one of the operation gas is drawn through the loop 25 by the pump 43 and, rather than being returned to the airway tap 23, is directed to the outer chamber 55 of the assembly 57. During this time gases within the bag 59 are thus forced through the valves 65 and 53 to the tap 23.

During the second phase of operation, gases from the loop 25 are drawn through the gas analyzer in the same fashion as during phase two of the first described mode of operation. However, when the captive bag assembly 57 is employed pump 43 is also utilized during the second phase to refill the bag 59. Thus during phase two of the operation utilizing the assembly 57, valves 41 and 65 are rotated 90ocounterclockwise and clockwise respectively and atmospheric air, or if desired some other gas, is drawn into the captive bag 59. When phase one recommences, the valves 41 and 65 are returned to their original position and the pump 43 is again operated in its forward direction.

Thus it is seen that the invention comprises apparatus whereby gas can be sampled from the airway and simultaneously returned to that airway in the same volume so that there is no net loss of gas volume from the airway. A conventional rapid gas analyzer can then be given adequate time to equilibriate and make a valid measurement of ECO2 in spite of the rapid respiration of the infant.

An important aspect of the invention is the utilization of a very small

internal diameter tube for the loop 25 such that when gas is drawn through the loop at a reasonable rate the flow is laminar with very little mixing of the gas. With this construction, if a gas of an undulating concentration is drawn into the loop 25 it remains in that undulating concentration throughout the length of the loop 25. The concentration of gas flowing from the opposite end of the loop will undulate in approximately the same wave form as it is admitted to the loop with very little slurring or mixing. It may be said then that the gases from the airway 13 are stored in analog form throughout the length of the loop 25.

CLAIMS: What is claimed is:

[*1] 1. In an apparatus for measuring expired gas concentrations of a patient, an airway adapted to be placed in communication with the patient's respiratory system, pump means having its intake connected to said airway for drawing a predetermined volume of gas therefrom to be sampled, a captive bag assembly having an outer chamber and a captive bag within said outer chamber, the interior of said captive bag defining an inner chamber, the exhause of said pump means being connected to one of said chambers and the other of said chambers being connected to said airway whereby the captive bag assembly replenishes the gas to the airway in the same predetermined volume and simultaneously with the operation of said pump means to draw gas therefrom.

[*2] 2. Apparatus as defined in claim 1 wherein said airway includes first and second taps, the intake of said pump means being connected to said first tap, said one of said chambers being connected to said second tap, and baffle means disposed in said airway between said taps for isolating the same.

[*3] 3. Apparatus as defined in claim 1 wherein said airway includes an elongated tube having an internal diameter sufficiently small in consideration of pumping capacity of said pump means to provide laminar flow therethrough and a length sufficiently great, compared to the lung volume and respiration rate of the patient, that the transit time of a gas particle through the tube is greater than the time required for several breaths of the patient.

[*4] 4. Apparatus as defined in claim 3 wherein said elongated tube has an internal diameter no greater than 1 mm. and a length of approximately 10 meters, said pump means having a pumping capacity of about 0.5 liter per minute.

[*5] 5. In an apparatus for measuring expired gas concentrations of an infant, an airway adapted to be placed in communication with the infant's respiratory system, an elongated tube, pump means in communication with said elongated tube for pumping respiratory gas therethrough, a gas analyzer, valve means having a first position placing said elongated tube in communication with said airway whereby gases from the respiratory system of the infant may be drawn into said elongated tube by said pump means, said valve means having a second position placing said elongated tube in communication with said gas analyzer whereby gases previously drawn into said elongated tube while the valve means was in its first position may be analyzed when said valve means is in its second position.

[*6] 6. Apparatus as defined in claim 5 wherein said elongated tube has an internal diameter sufficiently small in consideration of the pumping capacity of said pump means to provide laminar flow therethrough and a length sufficiently

grea, compared to the lung volume and respiration rate of the infant, that the transit time of gas particle through the tube is greater than the time required for several breaths of the infant.

[*7] 7. Apparatus as defined in claim 6 wherein said elongated tube has an internal diameter no greater than 1 mm. and a length of approximately 10 meters, and pump means having a capacity of about 0.5 liter per minute.

[*8] 8. Apparatus as defined in claim 5 wherein said pump means includes means for drawing a predetermined volume of gas from said airway through elongated tube when said valve means is in its first position, together with replenish means coupled to said airway for replenishing gas therein in the same predetermined volume and at the time said valve means is in its first position.

[*9] 9. Apparatus as defined in claim 8 wherein said replenish means comprises a captive bag assembly having an outer chamber and a captive bag within said outer chamber, the interior of said captive bag defining an inner chamber, one of said chambers being in communication with said airway and the other of said chambers being in communication with said elongated tube when said valve means is in its first position.

[*10] 10. Apparatus for measuring expired gas concentrations of a patient comprising pumping means adapted to be placed in communication with the airway of the patient for drawing a sample of the patient's respiratory gases, storage means in communication with said pumping means for storing the drawn respiratory gases in a sequence corresponding to the sequence that the gases are expired by the patient, a gas analyzer for analyzing said gases and valve means for interrupting the communication between said storage means and the airway of the patient and for simultaneously placing said storage means in communication with said gas analyzer.

207TH PATENT of Focus printed in FULL format.

3,785,370

<=2> GET 1st DRAWING SHEET OF 1

Jan. 15, 1974

DETECTION OF IMPAIRED PULMONARY FUNCTION

INVENTOR: Richards, Powell, Bayport, New York
Susskind, Herbert, Huntington, New York
Stang, Jr., Louis G., Sayville, New York

ASSIGNEE-AT-ISSUE: The United States of America as represented by the United States Atomic Energy Commission, Washington, District of Columbia (06)

APPL-NO: 289,204

FILED: Sep. 14, 1972

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US-CL: 128#2.08

CL: 128

SEARCH-FLD: 128#2.08, 2.07

REF-CITED:

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3,527,205	9/1970	*	Jones	128#2.08
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OTHER PUBLICATIONS

Meade, et al., "Automatic Measurement of Lung Function", The Lancet, Sept. 18, 1965, pages 573-575.

PRIM-EXMR: Medbery, Aldrich F.

LEGAL-REP: Anderson; Roland A.
Horan; John A.
Belkin; Leonard

ABST:
A non-radioactive tracer technique for detecting the presence of impaired pulmonary function indicating disease of the small airways at a much earlier stage than is permitted by previously used techniques, which non-radioactive technique involves the introduction of a bolus of helium at residual volume and the measurement of the concentration of helium in the expirate. The point in vital capacity where the helium concentration in the expirate increases sharply

above the alveolar plateau indicates the state of pulmonary function.
NO-OF-CLAIMS: 3

NO-OF-FIGURES: 2

NO-DRWNG-PP: 1

SUM:.

BACKGROUND OF THE INVENTION

It is known from studies reported earlier this century that lung ventilation is not evenly distributed. This unevenness has been attributed to regional expansion differences and various such regions have been postulated and identified. More recent studies have demonstrated convincingly that the principal regional variation in ventilation is vertical. Subsequently, the use of radioactive gas in a variety of techniques has made it possible to describe in greater detail the nature and extent of this uneven lung ventilation as well as to provide quantitative data in relation to this phenomenon.

From previous studies, such as those referred to above, it is known that there is a vertical gradient in ventilation distribution. Near RV (residual volume) most of the inspired gas goes into the upper parts of the lung and least to the lower. From zero to 25 percent VC (vital capacity), however, there is a progressive reversal in the distribution of inspired air until above 25 percent VC inspired gas is found to go preferentially to the lower lung zones, this distribution being essentially the same from 25 percent to 100 percent VC. This sequential behavior is explained by closure of some lower-zone airways at low lung volumes. The behavior is also found to be reversible; that is, during expiration, in the part of the breathing cycle from 100 percent VC to 25 percent VC most of the gas originates from the lower region whereas between 25 percent and zero VC most of the expiring gas originates from the upper region. These values will vary considerably with the age of a healthy person.

A unique advantage of radioactive-gas methods is that the regional concentrations of inhaled gas can be measured while that gas is in the lungs, and hence it has been possible to accurately locate the regions anatomically. Early work utilizing the radioactive gas <133> Xe established a vertical gradient in ventilation distribution. More recent work, reporting in greater quantitative detail the nature and extent of this distribution, is described in "Regional Ventilation of the Lung, Studies with Boluses of <133> Xenon" by Dollfuss et. al., Respiration Physiology (1967) 2, 234-246.

As a result of knowledge obtained from this line of work, some researchers have become interested in the application of this knowledge to determine impaired pulmonary function, such as for the early detection of emphysema, lung cancer, black lung disease, and other respiratory diseases. Unfortunately, the use of radioactive gases on a mass scale for the screening of large numbers of persons is not desirable because of the yet not fully understood long-term effects of population exposure to such levels of radioactivity. Also, in the case of a newborn infant, where breathing defects are sometimes difficult to detect and diagnose, and in the case of pregnant women, exposure of the patient to radio-activity is to be avoided except in clearly indicated situations. Further problems connected with radioactive-gas analysis techniques concern the

expense, the time consumed, and the shielding and other equipment which are required.

When a suitable tracer such as radioactive <133> Xe is injected into inspired air at zero to 25 percent of vital capacity and the presence of <133> Xe in the expirate is plotted against percentage of vital capacity, as shown in FIG. 5 of the aforementioned publication by Dollfuss et al., a sharp upward inflection in the xenon concentration is observed toward the end of a characteristically straight portion, known as the "alveolar plateau." This inflection point, expressed as percent VC, is believed to indicate distal airway closure. It has come to be recognized that effects due to aging, pulmonary inpairment due to disease of the small airways, and irritants such as tobacco smoke will cause the point at which this significant rise takes place to move to a higher percentage of vital capacity. Unfortunately, methods in use up to now employing radioactive tracers are not suitable for large scale use for reasons already noted; furthermore, they yield a curve with a break that is insufficiently distinct to be useful on any mass level for locating possible pulmonary impairment.

SUMMARY OF THE INVENTION

The invention described herein was made in the course of, or under a contract with the U. S. Atomic Energy Commission.

The present invention utilizes the uneven distribution of ventilation within a lung and employs a non-radioactive tracer for the detection of impaired pulmonary function.

In accordance with a preferred embodiment of this invention, a finite volume of non-radioactive tracer gas is injected as a bolus into the airway leading to the lungs undergoing investigation. The injection is made at 0-25 percent vital capacity, but most preferably at residual volume, that is, just prior to inspiration, and, during the next expiration, the expirate is monitored at the mouth for tracer content to determine the point in terms of percentage vital capacity at which there is an abrupt decrease in expirate coming from the lower portion of the lung as indicated by an abrupt increase in the percentage of tracer concentration. The location of this abrupt increase when compared by known computer techniques to what is normal for the age and size of the lung as determined from statistically obtained and stored information suitably computerized indicates whether there is any impaired pulmonary function requiring more detailed investigation. Inspiration of the tracer gas bolus at residual volume is believed to provide a better identified break in the curve during expiration than bolus introduction at a higher inspired air volume.

Thus a principal object of this invention is to provide a method of detecting impaired pulmonary function.

Other objects and advantages of this invention will hereinafter become obvious from the following description of a preferred embodiment of this invention.

DRWDESC:
BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a schematic illustration of apparatus useful for carrying out the principles of this invention.

FIG. 2 is a graph showing a curve produced for a subject in accordance with the principles of this invention.

DETDESC:

DESCRIPTION OF THE PREFERRED EMBODIMENT

A finite amount of helium is injected as a bolus into the passageway leading to the lungs just after forced expiration to the residual volume (RV), and the amount of air inspired is measured. The vital capacity (VC) and helium tension or concentration in the expired air at the mouth are then measured simultaneously and continuously and recorded, during the period of expiration immediately following inspiration.

Apparatus for accomplishing this is shown in FIG. 1 wherein is illustrated a mouthpiece 12 at the end of a tube 14 leading to a spirometer 16. A conventional syringe 18 injects into tube 14 a finite amount of helium when squeezed. A needle valve 22 (operated by a wheel 24) also terminating within tube 14 extracts some air from the latter for helium concentration measurement in helium detector 26. It is understood that a vacuum pump (not shown) in detector 26 continuously extracts a small sample from tube 14. The size of the sample may be controlled by wheel 24. Detector 26 produces a signal indicative of the instantaneous concentration of helium.

Spirometer 16 consists of double walled open top container 28 with a suitable seal 32 and an inverted container 34, the up and down movement of which thus controls the volume formed by containers 28 and 34. A pulley wheel 36 with a weight 38 and a cable 42 balances container 34. A potentiometer 44 mounted on the shaft of pulley wheel 36 produces a signal indicative of the position of container 34 and hence the volume enclosed.

The signals from potentiometer 44 and detector 26 go to an x-y recorder 46, as indicated by the broken line connections 48 and 52 to produce the graph of the type shown in FIG. 2. A computer may also be used, as shown.

In the use of the apparatus shown in FIG. 1, the subject, who may be a human being, breathes through mouthpiece 12 from a previously filled spirometer 16. At the moment that inspiration starts, which may be indicated by macimum volume of spirometer 16, a bolus of helium is injected into tube 14 by squeezing syringe 18. When the next expiration begins and a small part of the expirate passes through needle valve 22, x-y recorder 46 produces a curve such as that shown in FIG. 2.

The "break" in the curve, i.e., the first departure from approximate linearity, is found to be reasonably identifiable and thus capable of being recorded and compared with similar data accumulated for persons having similar age, size, weight, and other factors found to bear on this particular characteristic. The comparison of the location of the break in the curve with similar data accumulated as just described is or may be conveniently accomplished by using well known computer techniques for storing such information and making the appropriate comparisons desired taking into account normal deviations as is understood in the art.

The use of helium as the non-radioactive tracer is found to be particularly advantageous. Helium is believed to give greater sensitivity than other gases commonly used in these studies. Its low density and rapid diffusion rate ensure its rapid distribution in all the air passages of the lung. The low solubility of helium in blood minimizes corrections for solubility effects, its concentration in the alveolar gas depending primarily on alveolar ventilation.

It will be noted that the graph obtained for a particular subject only requires one breathing cycle, and no analysis or other treatment of the data is required other than to note the percent of vital capacity at which the break in the curve occurs. Thus, the method described herein is capable of economic widespread use on a large number of persons to locate whose who have some sort of an impaired pulmonary function which should be considered in greater detail, similar to the approach taken in mass X-ray screening to detect tuberculosis and related disorders.

In an example of this invention, a 1-cc bolus of helium was introduced into a subject's mouth just after forced expiration to his residual volume, utilizing the apparatus shown in FIG. 1. The subject employed was a 42 year old male, height 183 cm., and weight 84 kg. Detector 26 was a CEC Model 24-120B helium detector, spirometer 16 was a 9-liter Collins Model P-900, and recorder 46 a Hewlett-Packard Model 2D-2, all commercially available. The curve obtained is that shown in FIG. 2. The break at about 15 percent VS is relatively sharp and easy to identify. According to current theory the break indicates distal airway closure. A total of 300 test runs on 70 individuals, including the individual in the above example, produced reproducible data.

Helium can also be used in combination with other gases, and the timing of introduction of the individual gases, as well as the mode of introduction, i.e., as individual boluses or mixtures, to the inspired air can be varied. This improved method can provide the means of differentiating between, and determining the extent of, different obstructive diseases of the small airways. According to this method, individual boluses of helium and another gas are inserted into the passageway leading to the lungs during inspiration between residual volume and 25 percent vital capacity after which during expiration the percentage of vital capacity is identified as residual volume is approached at which point the abrupt increases in the concentrations of the helium and the other gas occur. The difference between the points of abrupt increases in concentrations for the two gases are compared and related to standards previously obtained for the two gases.

CLAIMS: What is claimed is:

[*1] 1. A method of detecting impaired lung function comprising the steps of,

a. supplying directly, to a passageway leading to the lung at 0.25 percent VC during inhalation, a bolus of helium and thereafter

b. measuring during expiration the helium concentration in the expirate to identify the point during expiration when an abrupt increase in the helium concentration occurs.

[*2] 2. The method of claim 1 in which the bolus in the amount of about 1

cc is inserted at residual volume of the lung.

[*3] 3. The method of claim 1 in which the point during expiration where an abrupt increase in the helium concentration occurs is detected and compared to statistically obtained information by computer to obtain evidence of the impaired lung function.